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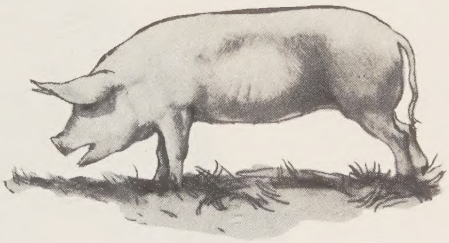

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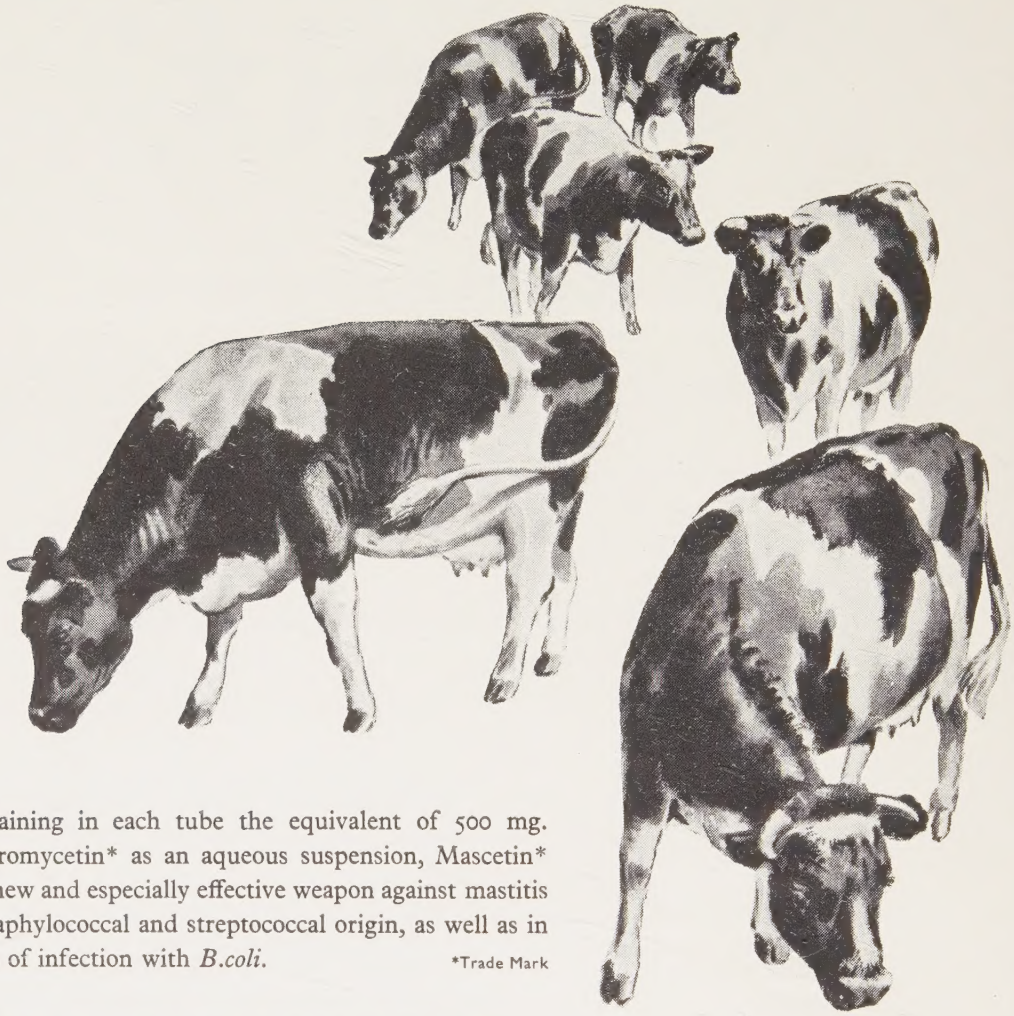

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CORRIGENDA -- Vol. 3, Part 2.

(a) page 101. In Table 2, the double-headed arrow referred to in footnote to table was omitted in error. The double-headed arrow should be inserted vertically, linking the words "Discrete lymphoid leucosis (lymphocytoma)" with "Lymphomatosis, Visceral".

(b) page 111, para. 2. The statement: "However, some British workers doubt whether strain R. P. L. 12 is a typical erythroleucosis (Darcel & Negroni, 1954)." should read as follows:- "However, a few British workers suggest that strain R. P. L. 12 may be an atypical erythroleucosis (Darcel & Negroni, 1954)."

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COMMONWEALTH BUREAU OF ANIMAL HEALTH

VETERINARY REVIEWS AND ANNOTATIONS

Volume 4 **April, 1958** *Part 1*

Immunity to Helminths

BY

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INTRODUCTION

The early work concerned with immunological reactions to helminth infection dealt mainly with diagnostic procedures. Such work was concerned with the employment in the field of helminthology of the then conventional serological techniques, generally applicable to bacteriology. Adequate reviews of the use and the value of such techniques have been given by Taliaferro (1929), Culbertson (1941) and Soulsby (1952).

Recently the mechanisms whereby a host is enabled to resist infection with a helminth as the result of previous infection have received increasing attention and these mechanisms form the main substance of this review.

That an animal may become immune to re-infection has been demonstrated with an extensive list of helminths, some of the more outstanding being Trichinella spiralis (McCoy, 1931), Strongyloides ratti (Sheldon, 1937), Nippostrongylus muris (Africa, 1931; Schwartz et al., 1931), Ascaris lumbricoides (Kerr, 1938a, b; Fallis, 1948; Sprent & Chen, 1949), Ancylostoma caninum (Otto & Kerr, 1939), Haemonchus contortus (Stoll, 1929), Trichostrongylus calcaratus (Sarles, 1932) and Dictyocaulus viviparus (Rubin & Lucker, 1956). All these have shed some light on the mechanisms by which the immune host antagonizes the normal development of the helminth. In general the antagonistic effects can be briefly summarized as follows, complete refractoriness to re-infection, the elimination of an existing infection, depression of growth, development

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and reproduction.

In the majority of cases it has been demonstrated that associated with the acquisition of immunity there is an antibody response which can be measured by the conventional serological techniques. It is also clear, however, that comparable antibodies can be induced in animals by the parenteral administration of helminth materials, either fresh or desiccated, but these antibodies will induce little or no protective immunity. This is one of the outstanding aspects of immunity to helminths, in that the conventional bacteriological techniques of producing artificial active immunity (i. e., the use of killed or attenuated materials) are not readily applicable to helminth infections. In the majority of attempts to induce immunity by the injection of fresh or dried parasite materials either only a low degree of protective immunity or none at all was produced, despite the fact that antibodies were developed. In general it is only when the living worm is allowed to invade an animal that substantial immunity is produced. Nevertheless protective immunity is associated with some circulating antibody since it is possible in many helminth infections to induce passive immunity with immune serum. This is evident in N. muris (Sarles & Taliaferro, 1936), S. ratti (Lawler, 1940), A. lumbricoides (Kerr, 1938b) and D. viviparus (Jarrett et al., 1955). Furthermore, the protective property can be transferred from an immune mother to its offspring both via the placenta and the milk, as instanced in the case of Hymenolepis fraterna infection in mice (Larsh, 1942).

It is therefore apparent that a multiplicity of antigens exists in the body tissues of helminths capable of stimulating antibodies which possess no protective characteristics. Nevertheless, some antigens do exist which have as their function the stimulation of protective immunity. Such antigens can be designated "functional antigens" and their homologous antibodies "functional antibodies", in accordance with the terminology used by Oliver-González (1946).

SELF CURE AND PROTECTION

A satisfactory point of departure for considering how the immune host repels or limits parasite infection is the observations of Stoll (1929) with regard to sheep nematodes. After infecting lambs with H. contortus and placing them on pasture Stoll observed that faecal egg counts rose to high levels. A few weeks later, however, there was a dramatic fall in egg counts to negative values, this being associated with loss of worms. Subsequently, despite frequent re-infection with large numbers of infective larvae the lambs remained refractory to re-infection. Stoll designated this phenomenon "self cure and protection". Essentially similar results have been reported in rabbits infected with Trichostrongylus calcaratus (Sarles, 1932) and T. retortaeformis (Michel, 1952a, 1953). Investigations in Britain on gastro-intestinal nematodes of sheep have shown that Stoll's findings are applicable on a flock basis (Soulsby, 1956, 1957a), and at this point it is of interest to consider how immune mechanisms modify naturally occurring helminth infections.

In Britain sheep normally undergo the "spring rise" phenomenon which is characterized by a marked elevation of faecal egg counts during

the spring, this being associated with an increased burden of nematodes. This phenomenon has been extensively investigated in Scottish hill sheep by Morgan and co-workers (1947, 1950, 1951, 1952) and in lowland sheep by Crofton (1954). Soulsby (1957a) found that the termination of the spring rise is associated with a definite immunological response which has all the characteristics of a group "self cure" mechanism. A similar situation exists in sheep in Australia when parasite burdens may be abruptly eliminated. Stewart (1950a) showed that this is an immunological reaction and depends on the availability of infective larval stages which in Australia may be present in large numbers on pasture only with the onset of wet weather. Subsequent to the group self cure causing termination of the spring rise a period of higher resistance to re-infection occurs in British sheep; this can be designated the period of protection and corresponds to that described by Stoll. This period of protection in sheep under natural conditions occurs at a time of the year when pasture contamination by infective larvae is relatively high (Crofton, 1952) as distinct from the position obtaining in late winter (Crofton, 1949). Despite the availability of infective stages, therefore, infection is maintained at a low level. Were non-immune sheep to be placed on such a pasture they should, unlike the flock which had undergone "self cure", be able to reflect the pasture contamination by acquiring heavy burdens of intestinal nematodes. This is in fact the case with lambs, these showing high worm egg counts during this period (Crofton, 1955).

The reasons for the onset of the spring rise in egg counts and worm burdens in sheep have been discussed by Soulsby (1957a). He suggested that this can be attributed to a depression of the immune status of the flock, citing as evidence the observation that before the onset of the spring rise a marked and persistent fall in antibody titre occurs. This depression of immune status is ascribed to the lack of stimulation by infective larvae, which, at this time of the year, are present on pasture only in very small numbers (Crofton, 1949). As early as 1932, Clunies Ross had shown that in the absence of re-infection acquired immunity would wane, immunity to intestinal nematodes being of a transient nature. Thus it can be envisaged that a falling immune status is to be expected during late winter in British flocks, and this would be in accord with the progressive decrease in antibody titres at this time recorded by Soulsby.

The origin of larvae destined to become adults participating in the spring rise is still a matter for debate, but the ability of larvae to remain dormant in the intestinal mucosa or elsewhere until conditions become more favourable for further development may have an important bearing not only on the origin of the spring rise but also on the pattern of parasitism by nematodes in general. Before dealing with this, however, it is desirable to deal further with the "self cure" mechanism.

MECHANISM OF SELF CURE

This mechanism is a spectacular response by the host resulting generally in the elimination of part or the whole of the parasite burden. It is possible that many helminth infections are partially or completely terminated by such a mechanism, especially those occurring in the bowel.

Infections where it has been unequivocally demonstrated are H. contortus (Stoll, 1929; Stewart, 1950b) Trichostrongylus spp. of sheep (Stewart, 1950c), trichostrongyles of rabbits (Michel, 1952a) and D. viviparus in cattle (Wetzel, 1948). Extensive investigations by Stewart have shown that it consists of a hypersensitive response in the abomasal or intestinal mucosa induced by the ingestion of infective larvae and which can also occur on the injection of larvae into the abomasum (Stewart, 1955). It should be noted, however, that larvae which stimulate the "self cure" mechanism may themselves develop to maturity (Stewart, 1950c). "Self cure" is, therefore, to some extent a misnomer and the term "crisis" might be more applicable. Some degree of cross reactivity occurs, in that Haemonchus larvae may induce "self cure" of intestinal Trichostrongylus spp. as well as Haemonchus infections, but the converse is not true (Stewart, 1953). Further investigations by Stewart (1953) showed that associated with the phenomenon there was a significant rise in blood histamine and if antihistamine drugs were given at the anticipated time of "self cure" the phenomenon did not occur. After "self cure" had occurred there was a rise in anti-nematode antibodies in the blood. This point is of particular interest, in that it indicates that high circulating antibody titres are not of importance in the causation of the "self cure" phenomenon. The phenomenon has been compared to the Arthus phenomenon by Soulsby (1957a). In the Arthus phenomenon local hypersensitivity is reflected by a circulating precipitating antibody and the degree of the local hypersensitive response is related to the amount of antigen applied. In the case of the "self cure" mechanism in T. retortaeformis infection in rabbits, Michel (1952a, b) found that the onset of the mechanism is related to the severity of the infection created and this may be construed as the amount of antigen made available for the initiation of the process.

Histological examination of the mucosa of animals which have undergone "self cure" reveals oedema and aggregations of eosinophilic leucocytes. It is of interest to note that comparable lesions are also seen in the intestines of animals parasitized by Trichinella spiralis (Larsh et al., 1956) and N. muris (Taliaferro & Sarles, 1939) and that a loss of worm burden is associated with the development of such lesions. It is not unlikely that these reactions represent a type of "self cure" which terminates the infection concerned and that "self cure" is a normal mechanism by which many intestinal parasites are eliminated.

The bowel mucosa inflammation evident in infection by both T. spiralis and N. muris is more rapidly induced in an immune animal and worm burdens are eliminated more quickly. In T. spiralis infection it has been possible to modify the bowel reaction by the administration of cortisone, which has a mitigating effect on hypersensitive states (Coker, 1955). When this is done the animal is enabled to retain the infection for much longer periods, indicating that local inflammatory responses are at least in part responsible for the elimination of burdens of helminths.

The actual mechanism which causes expulsion of helminths from the intestinal tract of an animal undergoing the type of "self cure" phenomenon described by Stoll (1929) and Stewart (1953) has not been clarified. Schmidt (1952) postulated that this had a mechanical basis, in that the release of histamine or histamine-like substances causes spasm of

smooth muscle with ejection of the parasites. As an alternative to this Soulsby (1957b) suggested that the local environment at the site of the "self cure" mechanism may become altered so as to make parasitism impossible. He suggested that this may be due to an alteration of the local oxygen tension, since such a consequence is seen in inflammatory processes (Campbell, 1931).

In addition to the effect on the parasitic population, the "self cure" mechanism may have undesirable effects on the host itself. This is instanced in the case of D. viviparus infection in cattle when the syndrome designated "fog fever" (Michel, 1954) may supervene, this being characterized by acute oedema and emphysema of the lungs and frequently resulting in the death of the animal.

The "self cure" mechanism in sheep would appear to be a reaction chiefly affecting the host, the parasites being eliminated almost as a secondary process. Whether such eliminated parasites are irrevocably incapacitated is unknown, and it would be desirable to know whether they could survive if placed in a normal host. In the case of N. muris, however, it would appear that at the time of elimination of the intestinal burden nematodes do suffer incapacitation, showing evidence of degeneration and other effects and it is reasonable to assume that these effects make them unable to persist in the mucosa.

INHIBITION OF DEVELOPMENT

In the "self cure" mechanism it is generally an adult population of helminths which is affected by immune processes. In other instances it can be unequivocally demonstrated that the major effect of immunity is on the development of larval stages. One aspect of this is the retardation of development to such an extent as to render larval stages "dormant". In many cases it is clear that this is the direct result of an immunological mechanism; in others, however, the retarded development or dormancy cannot be immediately ascribed to the conventionally understood immune processes. In some cases the retarded growth appears to be dictated by the presence of adult worms. Thus in the case of Trichonema spp. of horses the elimination of adult worms by drug therapy will allow groups of dormant larvae to emerge from the bowel mucosa and become mature (Gibson, 1953). This process can be repeated several times in the same horse. It can be envisaged that a lowering of the immune status of the animal will allow larvae to recommence development, but the part played by the adult worms in maintaining the immune status above levels which will allow larval development is unknown. Similarly with Haemonchus placei, a parasite of the abomasum of cattle, large numbers of larvae may remain dormant in the mucosa. On elimination of the adults, larval development is initiated and severe and even fatal infections may develop (Roberts, 1956).

The retardation of development of larval stages undoubtedly has very wide implications both in studies on immunity and also on the epidemiology of parasitic disease in animals. In this latter context it is possible for the patency of infections to be delayed for considerable periods and for clinical disease to occur under conditions of husbandry which would not

normally be associated with parasitic disease: such an eventuality has been recorded with stomach worms of cattle (Martin et al., 1957). Kotlán (1949) has designated the prolonged inhabitation of the tissues by larval stages the "histotrophic phase" and Taylor & Michel (1953) have discussed it in relation to retarded development of D. viviparus and other worms. There can be little doubt that retardation of development is a basic function of immunity and furthermore almost all effects detrimental to the parasite are essentially an interference with its metabolism. The intrinsic mechanisms of the antagonistic action of immunity on helminths are still unsolved to a great extent and much of the work on the serological aspects has failed to yield an adequate explanation. Upon infection of an animal with a given parasite a wide range of antibodies can be induced but many of these, by their very nature, cannot have protective value, in fact some may have the opposite effect. Thus, for example, in A. lumbricoides infection heterophile antibodies such as the Forssman antibody (Soulsby, 1958b) and blood group antibodies (Oliver-González, 1954) are induced.

Detailed examination of antibodies to ascaris by agar-gel diffusion techniques has shown that a multiplicity of antigen–antibody systems exists (Soulsby, 1957c; Kagan, 1957).

It is possible that a more biological approach will be necessary to elucidate these mechanisms, and for the present an examination of how immune processes affect the parasite will serve to explain to some extent how immunity antagonizes helminth development. One point of note in the retardation of development is that irrevocable inhibition of growth and development does not occur. This is clear in the case of the larval stages of Trichonema spp. and H. placei, since the removal of the antagonistic influence allows normal development to occur. In the case of N. muris inhibited in an immune animal, normal development will occur if such forms are placed in a normal animal (Chandler, 1936). This indicates that not only are immune processes responsible for the retardation but also their constant presence is required if inhibition is to be maintained. It would appear that a kinetic system is being inhibited which in the absence of its antagonist will function normally. This is distinct from the sensitization of a static entity which once sensitized does not require the further presence of the homologous antagonist.

MATERIALS WHICH STIMULATE IMMUNITY

It has previously been noted that living helminths in general induce the best protective immunity and the first indication that some material from the living parasite was essential in the production of such immunity was given by Sarles (1937), who observed that when N. muris larvae were placed in immune serum precipitates formed at and around the natural orifices of the larvae, namely the mouth, excretory pore and anus. Taliaferro & Sarles (1939) further demonstrated that "circumlarval" precipitates occur in vivo and considered these of great importance in retarding and halting the development of larvae in an immune host. Such precipitates have been demonstrated on a variety of nematode larvae when they are placed in homologous immune serum, the list including T. spiralis

(Mauss, 1940), A.caninum (Otto, 1939) and A.lumbricoides (Oliver-González, 1943). Mauss demonstrated that such precipitates on larvae reduced their infectivity by 60% after as little as one hour in immune serum. Soulsby (1957b), with regard to ascaris larvae, found that such precipitates were most evident at the excretory pore and suggested that materials emanating from the pore may represent the major part of the antigenic material for stimulating protective immunity in the host. These "circumlarval" precipitates are considered to be a reaction between antibodies and metabolic products eliminated by parasites from their natural orifices (Taliaferro, 1940). Such metabolic products collected from larvae may be used as antigens in the conventional serological tests, as in the case of T. spiralis infection (Sadun & Norman, 1956) and when injected into an animal will induce some degree of protective immunity. This has been demonstrated with N. muris in rats (Thorson, 1951, 1953), T. spiralis in mice (Campbell, 1955) and A. lumbricoides in guinea-pigs (Soulsby, 1957d). It has been suggested that such precipitates act mechanically by blocking openings. Thus Culbertson (1941) suggested that precipitates on the vulva of worms obstruct the passage of eggs, whilst those at the excretory pore block the excretory system. Soulsby (1957b), however, suggested that the antagonistic mechanism is more intrinsic and consists of a penetration by the antibody to within the parasite to inferfere with inner mechanisms, possibly enzyme systems. Some support for this view is provided by Schwabe (1957), who demonstrated that when N. muris larvae were placed in immune serum oxygen consumption was significantly reduced and this occurred well before the appearance of precipitates at the natural orifices. Schwabe suggests that the mechanism is the inactivation of an enzyme system responsible for oxygen utilization. In the absence of extensive information about the enzyme systems existing either within the body of the helminth or in the metabolic products no comprehensive assessment can be made as to what kind of anti-enzymic immunity might be expected to occur. Chandler (1953) favours the view that anti-parasitic immunity is anti-enzymic in nature. This view is very attractive and would explain to some extent why immunity induced by the use of dead and disintegrated parasites is inferior to that induced by active infections with living forms, since it is likely that the residue of enzymic protein is small in dead material. It is fairly certain that a vast complex of enzymes must exist in living helminths and they might be divided arbitrarily into "internal" and "external" enzymes. The internal are those responsible for the metabolism of the parasite such as those responsible for carbohydrate metabolism in which the Embden-Meyerhof sequence has been shown to exist (von Brand, 1952). Some of the external enzymes may be concerned with the preparation of food and others with invasion of and migration through tissues. In respect of the former Taliaferro & Sarles (1939) suggested that the excretions of the oesophageal glands (dorsal and subventral) play an important part in feeding and in the digestion of host tissues, and Chitwood & Chitwood (1938) suggested that materials from these glands may either be ejected through the mouth for extra-corporeal digestion or may be passed to the intestine for intra-corporeal digestion. Thorson (1956a) has shown that the secretions from the oesophageal glands of hookworms

contain proteolytic enzymes, the activity of which can be inhibited by serum from dogs immune to hookworms, and furthermore Thorson (1956b) has shown that extracts of the oesophagus of hookworms will, when injected into dogs, induce some degree of immunity. A lipolytic enzyme has been demonstrated in the metabolic products of N. muris larvae (Thorson, 1953) and this can be inhibited by immune serum. "External" enzymes presumably concerned in invasion and migration have been demonstrated in the invading cercariae of Schistosoma mansoni and the larvae of S. ratti (Lewert & Lee, 1956) where a collagenase-like enzyme assists in the penetration of the skin. Stirewalt & Evans (1952) have also demonstrated a hyaluronidase-like enzyme in S. mansoni cercariae.

TYPES OF ANTIBODY CONCERNED

If antiparasitic immunity has an enzymic basis then the quality of the immune response might be expected to change according to the stage of the infection and the tissue parasitized. Oliver-González (1941) demonstrated this with T. spiralis infection. He found that two distinct antibodies are induced on infection, one with an affinity for the adult worm in the bowel mucosa and another with an affinity for the larvae in the muscles. He suggested that this may be due to a variation in the enzyme requirements of the different stages, the enzyme systems being changed for each new substrate met with. He further observed that these antibodies with different specificities could be transferred passively and would protect against the specific phase. The protective property of the serum could not, however, be removed by absorption with adult or larval materials despite the fact that the conventional serological tests were rendered negative by this procedure. The protective antibodies were thus non-absorbable. Such non-absorbable antibodies have been demonstrated in other parasitic infections, two such being Cysticercus fasciolaris and Trypanosoma lewisi infections. With C. fasciolaris Campbell (1938) found two antibodies occurring on infection. The first, an "early" antibody, is associated with the migration of the hexacanth embryo and can be absorbed from serum by dried adult or larval tapeworm materials and can also be induced in animals by inoculation with such materials. The function of the early antibody is to protect the host animal against the invading hexancanth embryo. Later in infection a second antibody, the "late" antibody, appears which results in the death of established C. fasciolaris cysts. This "late" antibody cannot be absorbed by worm material and cannot be induced by inoculation. Campbell suggested that the second antibody is stimulated by the metabolic excretions and secretions of the parasite.

The non-absorbable antibody occurring in T. lewisi infection of rats is perhaps the most outstanding example of such an antibody and there are many aspects of immunity to T. lewisi which might reveal the intrinsic mechanisms of immunity to nematodes. The non-absorbable antibody in T. lewisi infections, called ablastin, has as its sole function the inhibition of mitotic division and growth of the dividing phase of the T. lewisi population. It cannot be absorbed from serum by dividing forms and such dividing forms are not sensitized by the antibody and will continue to

divide when placed in a normal animal. Ablastin is to be distinguished from the lytic antibody which occurs later in the T. lewisi infection and which can be absorbed by parasites and will sensitize them so that when they are placed in a normal animal they are destroyed (Taliaferro, 1948). Studies by Moulder (1948) have shown that ablastin will induce a change in the metabolism of glucose from that characteristic of reproducing trypanosomes, namely oxidative assimilation of glucose, to that characteristic of an adult population, namely the complete oxidation of glucose. It is interesting to note that the ablastin antibody in T. duttoni infection will inhibit reproduction of T. lewisi to some extent (Taliaferro, 1938), suggesting that both ablastins are directed against a metabolic system responsible for nuclear and cytoplasmic division. Recently Thillet & Chandler (1957) have been able to collect the "metabolic products" from a dividing lewisi population and have induced strong immunity with such materials. This is proof at least that the body of the parasite is not necessary for the production of ablastin antibody.

Since these non-absorbable antibodies are associated with living parasites it might be expected that some material from the living parasite would neutralize them. This has been shown to be the case with a protective antibody in N. muris infection which cannot be absorbed by ground up larval or adult materials but can be neutralized by the metabolic products excreted by larval stages (Thorson, 1954).

SPECIFIC STAGES CONCERNED IN STIMULATED IMMUNITY

As has been mentioned, if the basis of immunity is anti-enzymic in nature then enzymes will tend to differ according to the substrate in which the parasites find themselves. This phenomenon of adaptive enzymes is well known in bacteria. In their migration and development helminths frequently undergo changes in morphology, progressing from one larval stage to another and it is conceivable that some stages may be more important than others and that a relatively limited period in the developmental cycle may be of outstanding importance both in providing antigens which stimulate protective immunity and in inviting an antagonistic reaction. A striking demonstration of dependence on one specific stage for the production of protective immunity occurs in the case of Hymenolepis nana var. fraterna infections in mice. Such infections can be produced with or without a parenteral phase of the infection. When eggs are fed to mice cysticercoids develop in the intestinal villi of the host and immunity is produced. If, however, cysticercoids which have developed in beetles are fed, no parenteral phase occurs in the villi and no immunity develops (Hunninen, 1935). In other infections too it can be shown that a specific phase is responsible for stimulating protective immunity or that one stage in the absence of others will stimulate immunity. In the case of Schistosoma japonicum infection in monkeys Vogel & Minning (1953) were able to induce immunity by infections with exclusively male cercariae — this protected against cercariae of both sexes and indicated that immunity to schistosomes was not dependent upon the presence of eggs in the tissues. In a similar experiment with T. spiralis Anderson & Leonard (1940) induced a purely adult male infection of the bowel which resulted in

protection of the animal against a normal intestinal infection composed of both sexes and also protected against the muscle phase of T. spiralis infection. Further experiments with T. spiralis were conducted by Gould et al. (1955), in which infective larvae were treated with X-rays. The adults produced from the irradiated larvae are sterile but mice infected with the irradiated larvae were immune to re-infection with non-irradiated larvae. In the case of T. spiralis infection it is logical that, if patency of the bowel infection is prevented, no muscle invasion by larvae can occur; nevertheless such experiments do point to the phase of the infection which, when incapacitated, will alter the whole of the cycle of development.

Zaiman and co-workers (1953a, b, c, 1954a, b) have investigated extensively the bowel phase of T. spiralis infection using parabiotic union of animals. This technique is valuable in that, on infection of one member of the united pair with a parasite, the uninfected member will become immune if the substances which stimulate immunity are released into the lymph or bloodstream and carried to the uninfected parabiotic twin. This technique had been previously used by Chandler (1935) in an attempt to decide whether immunity to N. muris was of a local or general nature; Chandler was unable to demonstrate any immunity in the uninfected twin. Zaiman and his colleagues showed that immunity to both intestinal and muscle phases can be induced in a non-infected animal by blood-borne materials. Further experiments showed that exposure of the uninfected parabiotic mate to the first 5 days of an infection was adequate to increase its resistance but if this time was reduced to 4, 3 or 2 days then immunity was not produced.

Work such as this suggests two possibilities: either that between the fourth and fifth day after infection a specific "functional antigen" is released which is absent in previous stages, or that at this time more antigen is released than in the earlier stages. Further work is needed to discover whether the differences are qualitative or quantitative.

Soulsby (1958a) investigated the concept that a particular stage may be of importance in stimulating protective immunity. Working with A. lumbricoides in guinea-pigs he found that the period of 4 to 5 days after infection is likely to be of importance for the liberation of antigens which will stimulate protective immunity. This phase of Ascaris infection in the guinea-pig is also associated with the moulting of larvae from the second to the third larval stages and Soulsby suggested that the process of moulting may be of importance both by providing antigen to stimulate immunity and as a process to be antagonized by the immune mechanisms. Stages in the life cycle of Ascaris earlier than four days after infection appear to be of little importance either in stimulating immunity or in being affected by the immune processes. Even in a highly immune animal these early stages are allowed to enter, to persist for a few days and even to grow to a slight extent. Using a natural marker antibody Soulsby (1958b) found that the period of 4 to 5 days after infection was the earliest time at which a large release of antigen could be expected; this period again coincided with the initiation of the moulting process. It is interesting to note that inhibition of larval development occurs at a late larval stage (Michel, 1952b), suggesting that growth is allowed to occur up to the point

where the moulting process is initiated but is then halted until environmental conditions allow moulting to occur.

PROTECTIVE MECHANISMS OF THE PARASITE

The means by which helminths protect themselves from the host is a field of study which may explain some aspects of immunity to helminths. Becker (1953) discussed this and suggested that polysaccharide components may play an important part. He points to the polysaccharide capsules of bacteria such as pneumococcus Type III and suggests that analogous mechanisms may occur in metazoan parasites. The cuticle of helminth parasites deserves special mention since it is presumably this which prevents the parasite being digested by the host. Taliaferro & Sarles (1939) expressed the opinion that the cuticle of nematodes is impervious to inflammatory materials and Taliaferro (1940) suggested that it is also impervious to antigenic materials. Oliver-González (1943) modified this view by suggesting that although the cuticle is non-reactive in immune animals antigenic materials may diffuse through it particularly when the parasite has been previously damaged by immune mechanisms. Although it is possible to demonstrate antibodies on the surface of the cuticle of larvae which are migrating in an animal, such antibodies appear to have no detrimental effect on the larvae (Coombs & Soulsby, 1957). It would be interesting to know whether larvae inhibited in their development and dormant in the tissues have their cuticle coated with antibodies, but, *in vitro*, the location of precipitates at natural orifices suggests that the orifices are the weak points in the defence system of the worm.

UNUSUAL REACTIONS

An interesting, but as yet unexplained, phenomenon is that certain worms induce antibodies closely related to the blood group antibodies. Oliver-González (1954) found that parasites such as *A. lumbricoides*, *F. hepatica* and *T. spiralis* possess substances closely related to the blood group A substance of man and infection of rabbits with these parasites will induce high levels of A antibody. Coombs & Soulsby (1957) also demonstrated that on infection of blood group O pigs with *A. lumbricoides* elevation of anti-A antibodies occurs. Under natural conditions the anti-A antibody levels of pigs vary considerably throughout the year (Goodwin & Coombs, 1956) and it is possible that naturally occurring *Ascaris* infection in pigs may be responsible, in part, for this. Such blood group substances have not been searched for in the intestinal strongyles of sheep or cattle, but such a search might be worthwhile since Stone (1956) found that iso-antibody levels of cattle fluctuate considerably during the seasons of the year.

It is conceivable that the possession of a particular blood group by an animal may be detrimental to it as far as parasitic infection is concerned. This is illustrated in the case of the malaria parasite of man, *Plasmodium falciparum*, in which Oliver-González & Torregrosa (1944) suggested that human blood group A substance occurs and is the basic cause of the haemolytic manifestation of malignant tertian malaria. Butts

(1945) and Gear (1946) suggested that the blood group-like substance of the malaria parasite stimulates antibodies to itself and these then cross-react with the patient's red cells and, in the presence of complement, lead to haemolysis. An interesting observation was made by Oliver-González (1953) when he showed that polysaccharides, particularly blood group substances from parasites such as A. lumbricoides and T. spiralis, can become adsorbed to red cells and thus alter the specificity of the cell. If this occurred in an actual infection by these parasites then new antigenic groupings might be introduced on to the erythrocytes and the host would produce antibodies against the new erythrocyte–polysaccharide complex and therefore against its own erythrocytes. The work of Baker & Douglas (1957) on the anaemia associated with chronic trichostrongylidosis in cattle is of interest in this connexion since these authors suggested that a possible cause of the anaemia is the production of an auto-immune anti-red cell antibody.

NORMAL MECHANISMS IN IMMUNITY

This review has dealt with the mechanisms of acquired resistance to helminths. There are, however, many instances where animals have a natural resistance to parasites, this natural resistance being absolute, partial or sometimes subject to modification by age or food. Absolute natural resistance is commonly seen, in that a given species of helminths is able to parasitize only a limited group of animals. Natural resistance does not appear to be a specific quality but instead is exerted with equal intensity and effect against a variety of often unrelated parasites. The development of natural immunity with age is seen in pigeons infected with T. spiralis. Matoff (1936) showed that while young pigeons were susceptible, older pigeons could not be infected. Despite the fact that natural resistance appears to be a general quality there are instances where it is possible to ascribe natural resistance to a specific property of the body. In the normal serum of many animals there are substances which will destroy the infective stages of parasites. Thus Culbertson (1936) demonstrated a cercaricidal substance in normal serum, and in many cases animals possessing such a serum property fail to become infected with cercariae which they thus antagonize. Sato (1933) described an "agglutination" of filariform larvae of strongyloides in normal serum; and the normal serum of many animals has an antagonistic action on many species of trypanosome (Laveran, 1902; Culbertson, 1935). Thus normal human serum will destroy all pathogenic trypanosomes with the exception of those infecting man, namely T. gambiense and T. rhodesiense. It is probable that substances in the blood with an activity against a wide variety of organisms are similar in nature to the natural antibacterial properties of blood investigated by Mackie & Finkelstein (1931). Investigations along these lines might, however, yield some information as to how organisms become susceptible to immune mechanisms.

SUMMARY

Immunity to helminths may be manifested by a complete refractoriness to infection, the elimination of an existing infection, as exemplified by the "self cure" mechanism, or the depression of growth, development and reproduction.

In general, satisfactory protective immunity can be induced only by the presence of the living worms within the host. The antigenic stimulus for the production of protective immunity appears to be provided by metabolic materials associated with the living worm. These metabolic materials, by themselves, will induce immunity and it is likely that antibodies to them function in an anti-enzymic manner. Protective antibodies are, in general, non-absorbable by preparations of tissues of parasites but may be neutralized by metabolic products of helminths.

Evidence is accumulating that certain specific stages of a parasitic infection may be of outstanding importance in stimulating immunity and in being affected by immune processes.

Retardation of the growth of larval stages may produce "dormancy" of larvae in the intestinal mucosa, these dormant larvae being able to resume development on the elimination of the concomitant adult worm population.

In addition to mechanisms resulting in protection of the host other phenomena occur. Some may explain the natural resistance of animals to certain helminths, some may be beneficial to the parasite whilst others such as the stimulation of blood group antibodies remain unexplained.

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Recent Developments in Bloat Research

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Since the writing of the previous review on bloat for this journal (Johns, 1956), two major bulletins on this subject have been published in the U. S. A. The review of Cole et al. (1945), which for a decade was the standard work on the subject, has been revised and published by the National Research Council of the U. S. National Academy of Sciences (1956). Lindahl et al. (1957b) have published their extensive work on the chemical, pharmacological and physiological properties of the alfalfa (lucerne) saponins in the form of a technical bulletin. The present review does not cover the material in these publications but discusses other work carried out since the author's previous review.

GENERAL

A considerable amount of effort continues in attempting to find the cause of bloat, mainly in the U. S. A. and New Zealand. There are now two main schools of thought on the basic cause of bloat in ruminants:

(a) those who consider that the ailment is due primarily to a foaming of the contents of the rumen and reticulum;

(b) those who base their investigations on the assumption that it is due to the presence of a toxic substance causing the inhibition of rumen movements and/or the eructation mechanism.

It could be that both play a part, but the former theory appears to be gaining the greater number of adherents (Colvin et al., 1956, Barrentine, Nichols (personal communication), and Ferguson & Terry, 1955). It has been shown in many parts of the world that antifoaming agents can control pasture bloat (Payn, personal communication, S. Africa; Flynn, 1957, Australia; Barrentine, Cole, personal communication, U. S. A.). The author is not aware of any recent work which indicates that bloat is due to an inhibition of rumen movements.

Reid (1957a), using the tympanograph on intact animals, observed that the rhythmic activity of the dorsal sac of the rumen was present at all stages of bloating. More recently, Reid (unpublished) has used direct recording with a pressure sensitive transducer unit in fistulated cows and has confirmed these results. The frequency of reticular cycles in the bloated animal appears little different from normal, while the strength of the contractions as judged by the pressure changes they cause appears to be within the normal range. Activity of the rumen is more difficult to assess. Pressure waves, which in the non-bloated animal can be recorded locally, are transmitted through the whole organ when it is filled with foaming ingesta and hence will be recorded at points distant from

their origin. Recording from a single point in the rumen of bloated cows is therefore almost valueless for determining changes in frequency of reticulo-ruminal movements. At least three points of recording in the reticulo-rumen have been used at this laboratory to distinguish between "ghost" and local pressure changes.

Lindahl et al. (1957a) noted, in "feed lot" bloat, that rumen movements are active in bloating animals and that the contractions appear to increase in frequency as the animals begin to bloat.

Bloat has in the past been classified into two distinct kinds: "foaming" and "free gas". Many people with considerable experience of the condition claim that both types occur in the field. However, Johns (1954) and Ferguson & Terry (1955) considered it doubtful whether there are these two distinct forms of bloat, and thought that the supposed differences were only degrees of foaming bloat. It seemed likely that the amount of free gas present was a function of the stability of the foam. That this is probably the situation is well illustrated by the description by Boda et al. (1956) of the condition of a cow which died from bloat after feeding on fresh lucerne tops. After death the animal was tapped with a trocar and cannula and only free gas escaped. However, when the rumen was slashed open with a knife, the ingesta were found to be extremely frothy. The authors state: "Had the rumen been opened with a knife at the start, one would undoubtedly have obtained the impression that no free gas was present as it would have escaped with the foamy ingesta. This case should help to clear up some differences in viewpoint regarding the importance of frothing in acute bloat on legumes. . . . We are of the opinion, therefore, that frothing is an important etiological factor in acute bloat on legume pasture".

Lindahl et al. (1957a) state that "feed lot" bloat is of the frothy type with a varying amount of "free gas" always present. They also found little relationship between the total feed intake by different animals and the degree to which they bloated. This observation was similar to the results obtained by Johns (1954), who found no correlation between the rate of intake or the amount eaten and the degree of bloat produced.

Few direct pressure readings have been made on bloated cows, especially of the pressure at which death occurs. Lindahl et al. (1957a) recorded pressures directly with fistulated animals, and rated 10–15 mm. Hg as slight, 25–35 mm. Hg as moderate and 45+ mm. Hg as severe bloat.

As to the cause of death in bloat, Phillipson (unpublished) has done a considerable amount of work on the effect of inflation of the rumen on blood pressure and concludes that at present there is no reason to reject the hypothesis that death from bloat is due to anoxia. In inflation experiments with some twenty animals under pentobarbitone or chloralose anaesthesia using air, carbon dioxide, nitrogen, or oxygen, he found that the final stage is characteristic of anoxia and occurs irrespective of the anaesthetic used. Violent fluctuations in blood pressure occurred and unless pressure in the rumen was released death soon followed. Sudden rises of blood pressure to over 200 mm. Hg were common and were probably due to the release of adrenaline into the blood in response to anoxia. Considerable variation was found from animal to animal in the ruminal pressure needed to produce the crisis. A pressure as low as

10 mm. Hg was occasionally sufficient. Usually animals withstood 30 mm. Hg but sometimes stood pressures up to 80 mm. Hg. Carbon dioxide or oxygen usually allowed greater pressures to be induced than nitrogen or air.

This supplements the work of Dougherty and co-workers (Dougherty & Habel, 1955; Dougherty & Meredith, 1955) on conscious sheep where it was also found that there was considerable variation among individual animals and day to day variation in the same animals in the pressure that could be tolerated in the rumen.

It has become evident, as was pointed out in the previous review (Johns, 1956), that both plant and animal factors are implicated in the aetiology of bloat. Not all animals bloat readily and not all legume pastures produce bloat in susceptible animals. Lindahl et al. (1957a), in their "feed lot" studies, have found that as in pasture bloat, there are highly significant differences between animals in their susceptibility: these differences could not be correlated with their feeding habits. "Feed lot" studies have the advantage over pasture studies that the composition of the feed can be kept constant and so eliminate one variable in the study of the complex ailment.

In the following sections the study of foam, its action in the rumen, and the animal and plant factors contributing to its formation, will be considered.

FOAM

If we accept the theory that the formation of foam in the rumen is the primary cause of the majority of cases of uncomplicated pasture bloat, it is still a problem to determine what properties of the foam should be studied in relation to the aetiology of the condition. It was pointed out by Johns (1956) and Reid & Johns (1957) that surface active compounds may be of two types:

(a) surface viscous compounds, e.g. proteins and saponins which yield highly stable foams, whose solutions show relatively little lowering of surface tension, and whose foam stability is correlated with high surface viscosity:

(b) compounds whose solutions exhibit low surface tensions, e.g. soaps, which form less rigid foams and have low viscosity. The foaming properties of their solutions are related to their low surface tension.

The foam in the rumen appears to be of the stable high viscosity type.

Nichols et al. (1956, 1957) found that periods of increased and excessive frothing following changes from lucerne hay to fresh clover were associated with periods of high surface tension and viscosity. If the foaming compounds present had been of the low viscosity type, a reduction in surface tension would have been expected.

Contrary to the statement of Clark (1948) that antifoaming agents, e.g. turpentine, commonly used in control of bloat, increased the surface tension of rumen fluid, Blake et al. (1957) found that all such agents, including silicones and turpentine, decreased the surface tension of rumen fluid. This is not unexpected as substances which reduce surface tension

act by displacing the high viscosity type of foaming compounds from the surface layer, perhaps giving rise to an unstable foam.

It is apparent that surface tension measurements of possible foaming agents are not relevant in a study of the foaming properties of rumen fluid.

Mangan (1958a) has pointed out that there are a number of properties of high viscosity foams that can be measured, e.g. foam expansion, viscosity, static and dynamic stability, bubble size, static and dynamic interfacial tension and interfacial viscosity. Some of these are difficult determinations to carry out on a routine basis, and their relationship to bloat is not obvious.

Pounden et al. (1956) have measured what they term "foam capacity" and "foaming mass capacity", while Jacobson et al. (1957) have given further details of their measurement of "ingesta volume increase" and "stable ingesta volume increase" in "feed lot" studies. Mangan (1958a) has devised an apparatus for the measurement of foam expansion, dynamic foam stability and foam strength. Measurement of foam expansion and dynamic foam stability (dependent on the volume of foam produced) have not given much useful information. Two foams of quite different appearance (particularly bubble size) can give almost the same figure for dynamic foam stability. Foam strength measurements appear to be the most useful. As the rumen is in a state of more or less continuous movement, it would be expected that for a foam to persist it must have a considerable resistance to mechanical stress.

Mangan (1958b) has found that the strength of the foam formed from rumen fluid is dependent on pH. The pH optimum for maximum foam strength is about 6. The properties of these foams are readily studied with rumen fluid only from the animal whose ingesta have not yet markedly foamed, since the foaming properties of this type of compound are dependent on the foam-producing substances remaining in the un-denatured state. Once these substances foam they denature and the liquid drained from a formed foam cannot be satisfactorily foamed again. Hence liquid obtained from the foam in a bloated cow cannot be used to correlate bloating with the foam strength as determined in vitro.

However, the foaming properties of pure substances can be studied in relation to the properties of rumen fluid foams of less than full bloating characteristics.

ANIMAL FACTORS

(A) Saliva. In considering the role of saliva, research workers have often failed to take into account the fact that there are at least three components of mixed saliva with very different properties:

(a) The parotid secretion is continuous and watery, high in bicarbonate (0.1M) and in buffering power, with little protein present.

(b) The submaxillary glands secrete only during the taking of food. The saliva is viscous, much lower in bicarbonate (0.01M) and in buffering power, but contains a considerable amount of mucoprotein with strong foaming properties (Mangan, unpublished).

(c) The residual secretion (chiefly sublingual) combines the properties of the two mentioned above, being intermediate in protein and bicarbonate levels.

A large secretion of saliva, could, according to its composition, either assist in preventing bloat by buffering a fall in pH, or increase its severity by adding to the CO_2 evolved and by assisting in foam formation. One litre of parotid saliva secreted at pH 8.2 releases approximately 2 litres of CO_2 when it enters a rumen whose contents have a pH of 6.0.

Phillipson & Reid (1958) have found that there are individual differences in response in saliva flow to pressure in the rumen. Their results with five sheep and five calves can be summarized as follows:

(1) Pressure in the rumen usually causes a marked increase in the rate of secretion of the parotid and submaxillary glands and in the residual saliva flowing from the mouth.

(2) The pressure required to produce this effect varies from 8 to 20 mm. Hg.

(3) Once stimulation has occurred, further increases in rumen pressure cause inhibition of salivary secretion.

Occasionally the submaxillary and residual secretions have responded without any effect being found in the parotid secretions and vice versa. Some animals have not produced any increased saliva flow in response to rumen pressure stimulation.

It has been found in our laboratory (unpublished results), in a 5-month-old calf, that the amount of CO_2 necessary to raise the pressure in the rumen by 10 mm. Hg was much less at higher than at lower pressures, as shown below.

Pressure increase in rumen in mm. Hg	Volume of CO_2 required in litres.
2.5 – 10	20.8
10 – 20	4.8
20 – 30	2.7
30 – 40	2.2

Hence with an animal whose saliva flow increases in response to rumen pressure, it may well be that when mildly bloated, the extra CO_2 contributed from saliva could tip the balance in determining whether bloat is severe or not. As mentioned above, Lindahl et al. (1957a), in "feed lot" bloat studies, have made direct pressure readings on bloated animals. The pressure range within which stimulation of saliva flow occurs (8–20 mm. Hg) is classified as slight bloat by these authors.

Mangan (unpublished) found that the composition of pressure-stimulated parotid saliva differed little from that of normal parotid saliva, but that pressure-stimulated submaxillary saliva showed a fivefold increase in the concentration of the foam-producing mucoprotein as compared with the normal value.

It appeared that one of the individual differences between animals in susceptibility to bloat could be a consequence of differences in saliva composition. Preliminary results obtained in this laboratory in a study

of the electrophoretic patterns of submaxillary mucoproteins show that possibly there are inherited differences in ruminants. It has been observed that the pattern within a set of identical twin cows is similar and that the patterns between different sets of identical twins vary (Lyttleton, unpublished).

The realization of the full implications of these saliva studies in bloat aetiology, especially with regard to individual differences, must await the results of further work.

(B) Bacterial polysaccharides. Jacobson et al. (1957), in "feed lot" studies, calculated the percentage of encapsulated micro-organisms present and over an 8-week period obtained a correlation coefficient of 0.94 between the percentage of encapsulation of micro-organisms and the occurrence of bloat. This is of considerable interest since Hungate et al. (1955) suggested that slime production by bacteria may be associated with frothy bloat.

Dain et al. (1956) have studied slime production in Streptococcus bovis, an organism which occurs in considerable numbers in the rumen of sheep and cattle. They reported that this organism produced mucoid colonies only on sucrose agar and only in the presence of CO_2 and suggested that dextran formation was responsible for the sliminess of the colonies. On glucose the organism forms a capsular polysaccharide composed of galactose, rhamnose and probably galacturonic acid units (Hobson & MacPherson, 1954).

Bailey & Oxford (in preparation) have shown that the slime is a polyglucosan similar to the dextran produced by Leuconostoc species and that in liquid cultures also, there is an absolute CO_2 requirement for dextran production. The polysaccharide is, like the Leuconostoc dextran, produced only from sucrose, and with maximum yield in the pH range 6.5–7.0. In liquid media the dextrans exist free in solution, probably as a dextran-protein complex, giving very viscous cultures.

Str. bovis is present in large numbers in the rumen fluid of cows on legume pasture at this station. Bailey (unpublished) has found that the sucrose content of rapidly growing red clover is between 3.0 and 4.0% of the dry weight in leaf and stem.

Work is not yet complete on the determination of any difference in dextran production between bloating and non-bloating animals.

(C) Eructation Mechanism. Colvin et al. (1956) have devised a method whereby it is possible to determine the magnitude as well as the frequency of each eructation in cattle. The technique involves exposure and transection of the trachea followed by the suturing of the ends of the trachea to the exterior. The belched gas is conducted to a spirometer through a system of hoses which are connected to an airtight mask over the muzzle and a plastic cannula inserted in the cephalic end of the sectioned trachea.

It was found that when lucerne tops were fed, belching frequency was at a very low level and the amount per belch was greater than when the animals were fed oat hay or lucerne plus oat hay. The authors consider that this was due to the fact that lucerne tops contributed to the formation of a stable foam in the rumen which tended to block the cardia, whereas

with oat hay the gas was belched as rapidly as it was evolved. That froth appears to be an important factor preventing eructation was also suggested from their trials in feeding succulent legumes in which froth formation was prevented by the intra-rumen administration of "Wesson" oil.

The lowered frequency of eructation found by Colvin et al. (1956) on lucerne tops was not found by Johns (1954) and Reid (1957a) in the earlier stages of bloat on red clover. However, as bloat becomes more severe there is no doubt that eructation becomes less frequent until it ceases almost entirely.

It is possible that the technique employed by Colvin et al. (1956) may have interfered with the innervation of the oesophagus and made the eructation pattern abnormal.

Evidence has been obtained that foam can inhibit eructation. Dougherty (1956), using the isolated reticular pouch preparation in high level decerebrate sheep (thalamus intact), demonstrated the inhibitory effect of liquid on the opening of the cranial oesophageal sphincter. A number of experiments using this preparation were carried out in the author's laboratory in collaboration with Professor Dougherty, to determine whether foam could inhibit eructation by this means. Various foams were introduced into the pouch and gas passed in and the frequency and size of belches measured. Evidence was obtained that the reflex receptor controlling the opening of the cranial sphincter could distinguish between free gas and foam as the latter caused inhibition of belching. Considerable difficulty was experienced in obtaining a foam of sufficient strength for these experiments, and when the foam partially drained to give some free liquid present, changes in eructation activity occurred to give infrequent belches of large volume. This pattern appeared to be similar to that of Colvin et al. (1956) as described above.

The mechanism for clearing the cardia in the cow to allow gas to be eructated is still not clear despite the advances made with sheep by Dougherty and his co-workers using cinefluorographic techniques. In 1955, Dougherty & Meredith described a sequence of events preceding eructation in sheep. An important phase in this sequence is the holding back of the ingesta by the rumeno-reticular fold, after it has been thrown back by the double contractions of the reticulum. This movement was followed by a relaxation of the relatively empty reticulum, the contraction of the rumen to move the gas forward around the cardia and into the relaxed reticulum and the relaxation of the cardia and diaphragmatic sphincter.

Reid (unpublished) has found evidence suggesting that the damming back of the ingesta in the cow is achieved by the anterior pillar rather than the rumeno-reticular fold. Following a reticular contraction the pillar contracts and rises upwards and backwards towards the dorsal sac. If no belch is to occur before the next double contraction of the reticulum, the pillar sinks back to its relaxed position. If, however, a belch is to follow, the pillar recedes only partly, then contracts fully again, rising at the start of the rumen eructation movement. This behaviour of the pillar is, however, by no means invariable.

Reid (unpublished) using transducer units and a four channel Sanborn recorder has made a detailed study of eructation in cows and sheep by

recording at various points in the reticulo-rumen. It has been found that

(a) Although belching often occurs following the reticular contractions (as described by Dougherty & Habel, 1955) it may also occur at any point during the interval between successive reticular double contractions.

(b) Two distinct belches, each consequent on a pressure wave in the dorsal rumen, may occur during the interval between successive reticular double contractions.

It is concluded that an additional mechanism to that described by Dougherty & Habel must exist for the freeing of the cardia to permit eructation in the interval between reticular contractions.

PLANT FACTORS

The chemical composition of plants is important in bloat from the points of view of

(a) the supply of the substrate for fermentation which leads to gas production;

(b) the addition of foaming and antifoaming agents to the rumen fluid;

(c) the presence of possible toxic compounds.

(A) Fermentation substrates. Rosen et al. (1956) have studied the effect of the carboxylic acids of lucerne on gas production by rumen microorganisms and considered their relationship to legume bloat. They found that the magnitude of large "gas bursts" from lucerne could be correlated with the content of malic, malonic and citric acids in the extracts. They suggest that the bloat-provoking power of lucerne may result from the relative abundance therein of substrates available for microbial decarboxylation. The consequent release of large amounts of CO_2 (which may be trapped in foam) may be a major factor in the aetiology of legume bloat.

Mangan & Johns (1957), in a study of bloat-producing and non bloat-producing samples of red clover, could find no correlation between the concentration of sugars and organic acids in these samples and their bloat-producing potency. In this study, only a limited number of samples were analysed and an omission in the analysis of readily fermented material was the determination of starch. Bailey (in preparation) has found that this can constitute up to 4.5% of the dry matter of red clover.

Mangan & Johns (1957) point out that the apparent lack of correlation of sugar and organic acid level with bloat may mean that their levels are high enough to produce ample gas and volatile fatty acids to give rise to bloat when the complication of foaming is also present. It appears likely that as bloat is such a complex entity, with both plant and animal factors playing a part, correlation of carbohydrate content with bloating would be observed only within a certain concentration range and provided all other factors are optimal.

Cooper (1957) has postulated, without giving any factual evidence, that bloat is due to an imbalance in the ratio of nitrogen to phosphorus in the plant and in particular to deficiency of phosphorus. This theory appears to be pure speculation.

(B) Foaming compounds. Saponins and proteins are the only plant constituents that have been considered as contributing to foaming in the rumen.

Mangan (1958b) has studied solutions of saponins and proteins to determine the conditions for the formation of foams of maximum strength. The pH optimum for saponins (red clover and lucerne) was found to be 4.5—5 whereas cytoplasmic protein of red clover has a pH optimum of 6.

The protein optimum corresponds to the pH optimum for maximal foam strength for rumen fluid taken after ingestion of clover. At pH 6, saponin foams have little strength. This, coupled with the fact that bloat can be produced on high protein grass (Reid & Johns, 1957), would indicate that saponin does not play a major role in the aetiology of the condition while protein may well play a part.

Against this however, is the finding of Jacobson et al. (1957) that lucerne saponin and glucose can greatly aid in the formation of stable froth in rumen fluid.

Boda et al. (1957b) have produced moderate bloat in cattle eating dehydrated lucerne by the introduction of fresh egg white into the rumen. The bloat resulted from the formation of stable foam within the rumen, which reduced the frequency of eructation for the first 90 min. after administration of the egg white. The progressive rise in rumen pressure to 15 mm. Hg which occurred could be prevented by the simultaneous administration of vegetable oil. That egg white will produce bloat does not prove that the causative factor is a water soluble protein but suggests that protein may be an important factor in the aetiology of bloat on legumes.

Chemical methods for determining the concentration of foaming and antifoaming constituents are not available for the routine handling of a large number of samples. Hence Mangan & Johns (1957) devised a serial dilution technique for comparing the foaming properties of extracts of bloating and non-bloating clover. The crude plant macerate was fractionated into extracts containing

(1) soluble protein, "Saponin", and chloroplasts
(2) soluble protein and "Saponin"
(3) "Saponin."

When tested under optimum conditions of pH and salt concentration, none of these fractions showed any relationship in foaming properties with the bloat-promoting potential of the fresh clover. Hence it seemed to the authors that the difference between bloating and non-bloating herbage is unlikely to be due entirely to any difference in concentration of particular substances in the herbage. Rather will it be due to the amount of the particular substances released from the ingested herbage within the first 30 min. after eating. This may well be related to the physical nature of the plant material.

Ferguson & Terry (1955) and Mangan & Johns (1957) found that heating or drying largely destroyed the foaming properties of the "saponin" and protein fractions. Hence it appears important that any attempt to fractionate plant material for foaming compounds should be made on fresh herbage.

(C) Toxic compounds. Shaw & Jackson (1957) fractionated ladino clover

with several solvents and assayed the fractions for their physiological activity. The in vitro assay procedure suggested that ladino clover can contain at least two toxic substances, a choline esterase inhibitor, and an inhibitor of muscle respiration. They also found that intravenous injection into bulls and sheep of the aqueous fraction from ladino clover caused such symptoms as dyspnoea, respiratory failure, muscle tremors, muscular tetany and distension of the rumen.

Parsons et al. (1955) found that samples of rumen contents from cattle dying from acute bloat, and extracts from forages causing bloat, inhibited the mobility of segments of the isolated rabbit intestine. An extract of ladino clover that was known to cause bloat inhibited eructation in a fistulated cow.

These studies, together with the extensive work of Lindahl et al. (1957b) on saponins are of considerable interest for their own sake, but whether they have any direct bearing on the aetiology of bloat is questionable.

METHODS OF CONTROL

(A) Antibiotics. Barrentine et al. (1956) tried the oral administration of chlortetracycline, oxytetracycline, bacitracin, streptomycin and penicillin for the prevention of bloat in steers. Penicillin was the only antibiotic which prevented bloat without undesirable side-effects. They found that single doses of 50 mg. of procaine penicillin protected yearling steers from bloat for 1.5 to 3 day periods. Older animals required 50 to 70 mg. to prevent them bloating. The bloat-preventing effect of penicillin was produced only several hours after administration.

Thomas (1956) reported that a herd of 36 beef cows were divided at random and 18 dosed orally with 100 mg. of procaine penicillin. No bloating was observed in the treated group after 12 or up to 96 hours after dosing. Twenty-four cases were observed in the untreated group during a 48-hour comparison.

Johnson et al. (1956) fed 75 mg. of penicillin daily to a group of dairy cows for 10 days and reported that bloat was somewhat reduced by penicillin as compared with a control group, but that response varied greatly among animals.

Percival (personal communication), in a trial with identical twin dairy cows, found that procaine penicillin at the rate of 100–200 mg. daily was only about 50% effective in the control of pasture bloat. His results show differences in the response of individual animals to penicillin therapy.

In the author's experience with dry and lactating cows fairly effective control of bloat has been obtained by the use of 200 mg. of penicillin every 48 hours. Control was not 100% as there are some animals that do not respond to the treatment. However, it has been used fairly extensively in New Zealand and is considered by farmers to be a useful method of controlling bloat.

Work in conjunction with the New Zealand Dairy Research Institute has shown that at the dose level of 500 mg., procaine penicillin does not pass into the milk or affect the quantity or quality of the butterfat or milk

yield. No adverse effect on appetite has been noted but rather the reverse. The tendency is for penicillin-treated animals to eat more than the untreated. Cases have been experienced where milk let-down has been interfered with as a result of overeating.

A trial was carried out in which 3 pairs of identical twin heifers were used and one of each pair was dosed with 200 mg. of penicillin every 72 hours for six months. No deleterious effects on the treated animals were noted and there was no effect on milk yield.

One of the main drawbacks to the use of penicillin for bloat control in a large herd is the difficulty of administration. It can be mixed with a dairy ration or given in tablet form. Many cows will not take a dairy ration to which penicillin has been added, and have to be dosed. Barrentine et al. (1956) have used penicillin incorporated in a salt lick but this would not ensure even distribution of penicillin in a herd in New Zealand.

Penicillin appears to be of most use where a farmer wishes to treat a few cows in a herd or a whole herd for a short time.

A study of the effect of penicillin on the rumen fermentation has been made in this laboratory, using fistulated identical twin cows. When sampled at hourly intervals after the commencement of feeding (24 hours after dosing with penicillin) it was found that the rate of production of volatile fatty acids (and hence gas production) was considerably reduced over the first hours, while lactic acid and a reducing sugar accumulated temporarily. The breakdown of protein in the rumen was inhibited. There was a noticeable absence of froth on the rumen contents of treated animals and a characteristic brownish appearance was evident. The pH of the rumen contents of the treated animal did not fall as low as that of the untreated. After penicillin had been given for some 12 doses every two days, this inhibiting effect of penicillin on the rumen fermentation disappeared.

Though the rumen fermentation had become resistant to the action of penicillin, there still appeared to be some control of bloat though it was not complete. The treated animal tended to bloat moderately after eating and then deflate, while its untreated twin mate continued to bloat more severely.

When penicillin was discontinued for some 5 months the sensitivity of the bacterial fermentation to penicillin returned, though not as markedly as with the original dosings. More work on the use of penicillin in bloat control is needed before its usefulness can be assessed.

Whether antibiotics should be freely available to farmers for feeding to farm animals is a pertinent question that involves a much wider field than bloat prevention. This is outside the scope of this review but is a question on which there is considerable divergence of opinion (see Conference on Supplements and Additives in Animal Feeding Stuffs, Porter, 1957).

(B) Antifoaming agents. Nichols (personal communication) has screened some 250 surface active agents for their effect upon rumen fluid and micro-organisms and has concluded that there is no shortage of suitable agents. However, he also has come up against the problem of finding

practical ways of administering the compounds so that the period of their effectiveness in the rumen will amount to several hours.

Cole (personal communication) reported that oil administered before feeding controlled bloat for a short period.

Johns (1954) listed silicones as amongst the effective agents in bloat control and they have been widely sold commercially. The silicones tried at that time were dissolved in a paraffin and it could have been the paraffin that was the effective agent. Trials since that time with a large range of silicones, with and without various dispersing agents, have proved them completely unreliable in bloat control (Reid & Johns, 1957, and unpublished results). The reason for the ineffectiveness of the silicones is not at all clear.

Reid & Johns (1957) have found that bloat in cows on red clover could be successfully treated with antifoaming agents including vegetable oils, vegetable turpentine, emulsified tallow, whale oil, cream, lanolin, five grades of liquid paraffin and paraffin wax emulsions. Antifoaming agents giving variable results were a ricinoleic acid derivative, detergents and diethyl ether. Treatments without antifoaming agents failed to give relief.

Bloat was also prevented by the administration of antifoaming agents before feeding. However, protection lasted only for the feed following treatment and, except for greatly increasing the dose, no method of administration was found that would ensure protection at a subsequent feed. Hence the dosing of animals in the milking bail before depasturing did not appear to be a practical method of control. However, Payn, in South Africa (personal communication), has used the method very successfully under his particular circumstances. Payn divides his animals into three groups: (1) non-susceptible, (2) susceptible, (3) extremely susceptible. In his herd he finds 80% of the animals in group 1, 15% in group 2, and 5% in group 3. He found that three-quarters of an ounce of peanut oil was sufficient to give full protection to group 1 animals when pre-fed twice daily on maize meal before a morning and evening feed. When bloat was severe the daily dose was raised to two and a quarter ounces per cow, half being pre-fed twice daily.

Group 2 during the most dangerous period required three rations of one and a half ounces, a daily total of four to four and a half ounces per cow. Group 3 at the peak of bloat required daily 8–9 oz. oil per cow. With a decline in bloat severity these animals were treated as for group 2. Payn states that he is satisfied that no animal fed three-quarters of an ounce of oil will become an emergency case and works on the principle that when an animal bloats on the minimum ration, he doubles it.

This method of bloat control, which Payn has used successfully in South Africa, with an "on" "off" system of grazing, could hardly be used where labour is at a premium.

It is apparent that frequent dosing with small amounts of antifoaming agents would be the most satisfactory method of maintaining an adequate concentration of antifoaming agent in the rumen. This has been tried by the addition of antifoaming agent to the drinking water or by applying the agent directly to the herbage (Reid, 1955). Of the two methods, treatment of the water supply is the less reliable because of the variation in

drinking patterns from animal to animal and in the same animal from day to day. The spraying technique has been discussed more fully in the previous review (Johns, 1956).

It is obviously desirable that a material for therapeutic use in the field should not adversely affect the health of animals or the properties of milk or butterfat. The aim of a number of investigations (Reid, 1957b; McDowall, McGillivray & Reid, 1957; McDowall, Patchell & Reid, 1957; McGillivray, 1957; and McDowall, Reid & Patchell, 1957) has been to determine to what extent the various oils fulfil these requirements.

The agents chosen as having negligible ill-effects were peanut oil and tallow. The former has been quite extensively used for pasture spraying in New Zealand and in general farmers find that the cost is more than covered by the extra production compared with the level obtained from the herd when bloat is prevalent.

Emulsified tallow initially proved somewhat difficult to use as the emulsion did not remain stable during storage and contained small aggregates of unemulsified fat which block the strainer and nozzles of spraying appliances. However, these difficulties have been overcome by farmers in Victoria, Australia (Flynn, 1957) and good control of pasture bloat has been obtained by the use of emulsified tallow sprayed on pasture at a cost of about twopence per cow each day.

Pasture spraying in which the day's ration of pasture for the herd is divided off by an electric fence and the area sprayed with a boom mounted on a tractor remains the most certain method of bloat control practised in New Zealand.

SUMMARY

Foaming of the rumen contents is becoming more widely recognized as a major factor in the aetiology of legume and "feed lot" bloat. Two possible modes of action are (a) a direct inhibition of the eructation mechanism by foam and (b) the retention of the fermentation gases within the foam thereby preventing them being eliminated by belching. The foam formed in the rumen is of the stable, high viscosity type which has a pH optimum in the region of 6 for maximum foam strength.

Differences between animals in their susceptibility to the condition may be due to (a) a difference in rate of saliva flow in response to rumen pressure and (b) an inherited difference in saliva composition. No difference in chemical composition has yet been found between bloating and non bloat-producing legumes.

Two methods of controlling bloat in the field are (a) antifoaming agents (oil or tallow) as a pasture spray, (b) oral administration of penicillin. The former is the most reliable while the latter has its uses where a small number of animals is involved.

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Cutaneous Streptothricosis, Mycotic Dermatitis and Strawberry Foot Rot and the Genus *Dermatophilus* Van Saceghem

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Hudson (1937) made the suggestion that streptothricosis in cattle, which he had studied in Kenya, and mycotic dermatitis, described by Bull (1929) from Australia, were caused by closely related organisms and Snijders & Jansen (1955), in South Africa, have agreed with this. There has however been no formal taxonomic proposal bringing these two organisms together, and it is the purpose of this account to unite them in the genus Dermatophilus Van Saceghem along with the organism described by Thompson (1954) from strawberry foot rot in sheep.

The nomenclatural changes have been made only after an extensive survey of the literature and conform with the International Rules for the Nomenclature of Micro-organisms (Ainsworth & Cowan, 1954). An attempt has also been made to stabilize the common clinical names of the diseases.

STREPTOTHRICOSIS OF CATTLE

Nature of the disease

The disease was first described in cattle by Van Saceghem in 1915 in the Belgian Congo. He had seen it some years previously and it had probably been known for a very long time. The lesions consisted of small but confluent, raised, circumscribed crusts on the skin composed of epidermal cells and coagulated serous exudate with embedded hairs. Commencing as a localized condition, it could become progressive and sometimes prove fatal to the animal. Subsequent accounts have added little to the clinical description given by Van Saceghem, except to define the distribution of lesions over the body (Plowright, 1956; Zlotnik, 1955). The disease is thus essentially an exudative dermatitis followed by extensive scab formation.

Disease name

The name which Van Saceghem (1915) applied to the disease was "Dermatose contagieuse (Impétigo contagieux)" in the belief that it was transmissible by contact. At the same time Lane (1915) mentioned the existence of "Senkobo scab" in North-West Rhodesia and was followed by Armfield (1918) and Griffiths (1918), both of whom

described an unspecified dermatitis of cattle in several parts of Central Africa. "Contagious impetigo" and "Senkobo skin disease" continued to be used in most of the annual reports of the veterinary services of various African countries until 1926, when, in the report of the Veterinary Department of the Northern Province of Nigeria (Henderson, 1927), the name "streptothricosis" was first applied to this disease. It seems that this name was based on common (but unpublished) usage, following the suggestion of Hutchins (1919) that the disease was caused by a "streptothrix". Without further investigation it became adopted in almost all publications in English and was also used in those in French. In the 1923 report for the Northern Provinces of Nigeria the native name of "Kirchi" was first mentioned but, like "Senkobo scab" already mentioned, "Saria" used in Nyasaland by Curson (1920), "Drodro-Boka" used in Madagascar (Buck, 1948) and the "Uashin-Gishu skin disease" in Kenya (Hudson, 1937), it is possible that other skin diseases are included in the term.

Of these names "streptothricosis" alone was commonly adopted in both English and French for the disease in cattle, horses and goats in Africa, although "cutaneous actinomycosis", "cutaneous streptomycosis" (Chodnik, 1956) and "impétigo tropicale des bovidés" (Van Saceghem, 1934) have all been proposed.

The causal organism

So distinct was the organism found by Van Saceghem in the scabs from affected animals that he had no hesitation in creating for it a new monotypic genus, calling the new species Dermatophilus congolensis. In the scabs it occurred as branching mycelial filaments 1.4μ to 1.8μ wide, divided both transversely and longitudinally to form spores. The following year, Van Saceghem (1916a) reported its isolation in pure culture and described the growth of the filaments in serum broth. This was mycelial at first and was followed by the characteristic division and disintegration of the filaments into coccus-like forms. On agar a whitish-grey, viscous colony was formed. Van Saceghem gave more details of the growth in culture some twenty years later (1934) and for the first time described the biochemical characters of his isolates.

The relationship of Dermatophilus congolensis to other organisms and the validity of the name

Realizing the significance of having to create a new taxon, Van Saceghem tried to relate it to other organisms and place it in the appropriate group. At first he considered it to be a fungus but, on submitting preparations to Mesnil and Pinoy, he accepted their suggestion that it was a bacterium. He therefore related it to the filamentous bacteria and to the Cyanophyceae (blue-green algae), saying that its filamentous nature alone was not sufficient to distinguish it as a fungus. Later, in 1934, he deplored the lack of progress in the study of the organism and the disease and again considered the relationships of Dermatophilus congolensis. In this paper he defined it as a bacterium which existed saprophytically as a "tétragène" — Tetragenus congolensis Van Saceghem and in an invasive filamentous

form -- Dermatophilus congolensis Van Saceghem. On this occasion he referred the "tétragène" to Roubaud and Truché for confirmation.

No further studies on the organism from cattle appeared until Hudson (1937) described the disease in Kenya. He considered that Dermatophilus was closely related to Actinomyces on account of the filamentous growth in culture, and at the conclusion of his paper he suggested a new combination Actinomyces congolensis (Van Saceghem) Hudson.

With the organism placed in Actinomyces, one finds that the epithet had already been used for the species described as Discomyces congolensis (Baerts, 1925) and transferred by Brumpt (1927) to Actinomyces congolensis (Baerts) Brumpt. This was later considered by Dodge (1935) to be a Sporotrichum sp. but its status is uncertain.

Still further confusion was created by Velu & Barotte (1924), who classified Dermatophilus congolensis as Dermatococcus congolensis (Van Saceghem) Velu and Barotte. However, this name is antedated by Dermatococcus congolensis Van Saceghem (1916b) which had been isolated from ulcerative dermatitis in a horse and was a true coccus, not related in any way to Dermatophilus congolensis.

One of the curious things about the name of the organism arises from the early reference to a "streptothrix", and the later use of "streptothricosis" as the disease name. Apparently no one ever transferred the organism either formally or by suggestion to the genus "Streptothrix" until 1955, when Snijders & Jansen (1955) and Schulz (1955), in successive papers in the same journal, both used the binomial "Streptothrix bovis", without any formal citation or authority. That the use of this name is incorrect is quite certain, but in order to explain exactly why this is so it is necessary to show how the generic name Streptothrix has been used and misused.

The earliest use of Streptothrix as a generic name was by Corda in 1839. He created it for a hyphomycete he found growing on rotten wood. The name was validly published and the fungus is still known as Streptothrix fusca Corda. In 1875 however, Cohn used Streptothrix for a fine, filamentous fungus he observed in lesions of lumpy jaw in cattle and so his generic name was a homonym of Corda's (i.e., the same name applied later to a different organism). Unfortunately subsequent medical and veterinary workers have freely used Streptothrix Cohn for almost any fine, branching, filamentous organism found in lesions of man or animals and a tremendous amount of confusion has ensued. Chester (1901) was thus led to publish S. bovis (Harz) Chester as a new combination for the causal organism of lumpy jaw in cattle, and Foulerton (1901) used the trinomial S. bovis communis for the aerobic actinomycete he isolated from similar lesions. Thus there are now three invalidly named organisms bearing the name Streptothrix bovis (viz. those of Cohn, Chester, and Snijders & Jansen), and for the reasons outlined above the name cannot be used for Dermatophilus congolensis.

Three further complications require explanation before the name adopted here can be fully justified. Two of these appear to have arisen because of the ubiquitous occurrence of certain actinomycetes, viz. the Streptomyces spp. These organisms, whose position is discussed later,

are aerobic and are common in soil and in the air and consequently on the coats of animals (Ainsworth & Austwick, 1955). In 1935, Erikson described an actinomycete which had been isolated in Nigeria from streptothricosis in an ox as Actinomyces bovis Harz var. nigerianus Erikson (No. 4572). From the description and illustration this organism was probably a Streptomyces, possibly of the S. albus series, and was most likely a contaminant on the skin of the animal concerned. More recently Chodnik (1956) has isolated another actinomycete from cases of streptothricosis in cattle in the Gold Coast, which is again placed in the Streptomyces albus series, but on this occasion it was actually claimed to be the cause of the disease.

The third complication involves the date of publication of Dermatophilus congolensis, a name which has not escaped challenge on the grounds of priority from what appears to be an earlier spelling and hence valid name for the organism, viz. Dermatophylus [*] congolense, used by Van Saceghem in his paper in the Bull. agric. Congo belge Vol. 5, part 4, pp. 567–573 (1914). In almost all respects except for the name, this paper is the same as that published in the Bull. Soc. Pat. exot. Vol. 8, part 6, pp. 354–359 (1915), in which the spelling Dermatophilus congolensis is used. It was not clear which of these names Van Saceghem intended to use, until he published his further views on the disease in 1934, when he adopted the latter one, but it has been necessary to decide which name takes priority by an investigation of the dates of publication.

With considerable help these dates have been ascertained and leave no doubt that Dermatophilus congolensis was the earlier name despite its appearance in a journal dated 1915 whilst the other is in one dated 1914. What seems to have happened is that with the outbreak of the first world war, the Bull. agric. Congo belge was published in London instead of Brussels and Part 4 of Volume 5 was issued on or about the 3rd August 1915 (Van Saceghem's paper actually bears the manuscript date 15th January 1915). Part 6 of Volume 8 of the Bull. Soc. Pat. exot. however, containing the papers presented at the Séance of the 6th June 1915, was published in Paris on or about the 20th June 1915, and certainly not after the 28th June 1915 when the part was received by the publishers, Masson et cie., from their printers.

From this apparent confusion there emerges the single valid name for the organism isolated from streptothricosis lesions in cattle in Africa, i.e., Dermatophilus congolensis Van Saceghem (1915 emend. 1916 and 1934). All the other names suggested or used are either invalid according to the International Code of Botanical Nomenclature, 1956 and the International Code of Bacteriological Nomenclature, 1948 or are applied to other unrelated organisms.

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* An etymologically identical name is Dermatophylus Linn., which has been used for a genus of jigger fleas (Sarcopsyllidae) but is antedated by Tunga Linn.

MYCOTIC DERMATITIS IN SHEEP

Nature of the disease

Bekker (1928) directed attention to several apparently undescribed skin diseases of sheep in South Africa, and amongst them was a condition he referred to as "lumpy wool". This consisted of the development of exudate on the skin surface which hardened into pyramidal masses beneath the wool. The same year Seddon (1928), in Australia, called a similar disease "mycotic dermatitis" because he observed a fungus-like organism in the scabs and in 1929 described the condition in detail as an initial hyperaemia followed by scab formation without loss of wool. In rare cases the disease was progressive and ended fatally but generally recovery was spontaneous and a zone of exudate was left in the wool. When affecting the woolly parts of the skin in sheep the disease thus closely resembles streptothricosis in cattle in its exudative nature, but not in its clinical appearance.

Disease name

The name "mycotic dermatitis" for this disease in sheep has become widely adopted and the few exceptions to its use are common names such as "rain-rot" and "matted wool". It is however, like dermatomycosis, rather an unsatisfactory name in so far as any dermatitis of fungal origin can be termed "mycotic dermatitis" and hence ringworm may be included. Fortunately the name has become well-defined and is rarely applied to anything except this disease.

A further clinical condition appears to be associated with an organism of the type found in mycotic dermatitis. It was described by Nisbet & Bannatyne (1955) in sheep in Scotland as a "dermatitis" affecting only the hairy parts of the skin of the face, scrotum and legs. Hudson (1937) had also described similar lesions on the face and wool covered areas of sheep in Kenya from which he had isolated Dermatophilus congolensis.

The causal organism and its name

The first name applied to an isolate from mycotic dermatitis of sheep was Actinomyces dermatonomus Bull 1929. This organism was described as forming a laterally branched mycelium ($0.5\mu - 1.0\mu$ in diameter) which produced "conidia" (coccoid) and bacillary segments by means of transverse and longitudinal divisions. In the exudate from the skin lesions it occurred as short, divided mycelial and bacillary forms. In placing the organism in Actinomyces, Bull was influenced by the extensive formation of a narrow branching mycelium, both in culture and on the host, but he actually suggested that it might be related to Nocardia. Clarification of the relationships of the different groups of actinomycetes was not available until Waksman & Henrici (1943) classified the forms with a fragmenting vegetative mycelium into the Actinomycetaceae and subdivided these into the anaerobic Actinomyces Harz and the aerobic Nocardia Trevisan. Thus Nocardia appeared more suitable for Bull's organism and it was included in this genus by various

subsequent investigators. Henry (1952) was probably the first to use the name exclusively. Nisbet & Bannatyne (1955) used the name Actinomyces sp. for their isolates, which they considered were closely related to A. dermatonomus.

During the survey of the literature two mistakes in the citation were encountered. One was in Nannizzi's book (1934), where Actinomyces dermatonomus Oxer 1930 was used: the citation of this name was no doubt due to Nannizzi having consulted Oxer's paper (1930) on mycotic dermatitis in Tasmania. The other was found in the compilation of Hauduroy et al. (1953), in which the organism was cited as Actinomyces dermatonomus Oxer 1929, followed by the reference "Oxer. Bull. Aust. J. Exp. Biol. Med. Sci., 1929, 6, 301." Here the authors evidently mistook the name of L. B. Bull for the abbreviation for "Bulletin".

Thus the earliest name for the causal organism of mycotic dermatitis in sheep is Actinomyces dermatonomus Bull, 1929; and the organism was (informally) transferred to the genus Nocardia by Henry (1952) because it was aerobic.

STRAWBERRY FOOT ROT IN SHEEP

Nature of the disease

The first descriptions of strawberry foot rot appeared in 1946–47, when a series of papers on the condition and its transmission to experimental animals appeared, all the material having been obtained from outbreaks of the disease in north-eastern Scotland. Harriss (1948) described the development of the lesions from small heaped-up scabs on the skin of the leg to spreading wart-like scabs often reaching to 2–4 cm. above the knee. When extensive the exudate from the lesions formed a hard casing over the area and the coronet region was swollen and inflamed. On removal of the scabs a raw surface was exposed, which showed numerous bleeding points giving a superficial resemblance to a strawberry.

Disease name

"Strawberry foot rot" appears to be a name of local origin and does not seem to be attributable to any particular author. Various clinical names have been applied to the lesions in sheep such as "proliferative dermatitis of the legs" (Harriss, 1948), and the disease produced by Selbie & Robinson (1947) in rabbits by inoculation of material from sheep was called "infectious papillomatosis".

The causal organism and its name

Strawberry foot rot was first believed to be due to a virus by Selbie (1946) and Harriss (1948). With this concept in mind Abdusallam & Blakemore (1948) found that the infective agent passed through a 0.69 μ gradocol membrane and was present in the supernatant fluid from centrifuged suspensions of scabs, but they failed to obtain infection with Berkefeld V filtrates. These authors remarked on the presence of a filamentous organism resembling Fusiformis necrophorus in the exudate from experimental lesions on a

rabbit, but they did not isolate it. A considerable amount of immunological work was also carried out by these authors and by Horgan & Haseeb (1948) in attempts to show a serological relationship between strawberry foot rot and contagious pustular dermatitis, but the results were inconclusive.

Thompson (1954) first suggested the bacterial nature of the causal agent of the disease by the isolation of what he considered to be a Rhizobium sp. from both natural and experimental lesions. He described the organism fully and its characters agreed very closely with those of Actinomyces dermatonomus, although at the time no reference was made to this species. Thompson & Bisset (1957) however re-described Thompson's original isolate and in so doing, set up a new sub-order and family of the Eubacteriales to accommodate it, together with Actinomyces dermatonomus Bull. The generic name used was Polysepta, on account of the characteristic division of the filaments, and the strawberry foot rot organism was described as P. pedis Thompson and Bisset. Actinomyces dermatonomus Bull was transferred to the new genus as a new combination, P. dermatonomus (Bull) Thompson and Bisset. According to the International Code of Bacteriological Nomenclature these taxa are adequately described but no type species for the new genus was cited.

RELATIONSHIPS OF DERMATOPHILUS

The interrelationships of Dermatophilus congolensis, Actinomyces dermatonomus and Polysepta pedis

From their descriptions it is clear that the causal organisms of streptothricosis in cattle and of mycotic dermatitis in sheep are very similar both morphologically and in their pathogenicity. Support for this close relationship is given by their common difference from known bacteria and actinomycetes, viz. by the transverse and longitudinal division of their filaments, and they are well separated from the eumycetes both by this character and by the narrowness of their "hyphae". Further similarities lie in their habitat and the type of reaction which they evoke in their hosts. Moreover their ability to cross-infect and cause similar lesions in both cattle and sheep is further evidence of affinity.

Hudson (1937) first suggested this relationship and emphasized the differences between his own isolates obtained from lesions of cattle and the hairy parts of the skin of sheep, and A. dermatonomus obtained by Bull from the wool covered areas. Albiston (1933) had already made isolations from cattle for the first time in Australia and found that this strain differed from those from sheep in its greyish-white colour on solid media, its more rapid growth and in its greater virulence for experimental animals. There was no reference in this paper to the African disease in cattle. Further comparisons of the two organisms have been made by Snijders & Jansen (1955), who found that their morphological and biochemical differences were mostly the result of the more active growth of the isolates from cattle. No one has so far compared Dermatophilus congolensis with Polysepta pedis but the latter species has now been placed in the same genus as Actinomyces dermatonomus by Thompson &

Bisset (1957).

If, therefore, on the one hand Dermatophilus congolensis and Actinomyces dermatonomus are very closely related and on the other A. dermatonomus and Polysepta pedis are congeneric, it follows that Dermatophilus and Polysepta are different names for the same genus. Of these two names Dermatophilus Van Saceghem is the earlier and must have priority, so that Polysepta Thompson and Bissett is therefore a synonym.

Relationship of Dermatophilus to other micro-organisms

Although Van Saceghem at first considered Dermatophilus congolensis to be a fungus, his collaboration with other authorities led him to place it in the filamentous bacteria. Further suggestions on the relationship of the three organisms with the bacteria do not seem to have been made until Bisset & Thompson (1956) considered that in Polysepta pedis the "type of septation and the form of its coccal units are suggestive of a relationship with the true cocci".

Longitudinal division of this type, however, is also found in the algae, more especially in the Phaeophyceae (brown algae) where it is seen in the production of haploid and diploid multilocular sporangia, and in certain Chlorophyceae (green algae) which normally grow vegetatively by a similar method, e.g. Prasiola. In the eumycetes there are also genera in which longitudinal septum formation occurs, notably in the production of the muriform spores of Alternaria, but it is not suggested that Dermatophilus can be placed in either of these sub-divisions of the Thallophyta.

Dermatophilus may most easily be compared with the genera of the actinomycetes. The connexion with this group probably stems from the original observation of a "streptothrix" in the lesions on cattle, but no serious proposals were made to this effect until Bull and Hudson studied cultures. The main grounds for inclusion were the colony form and the extensive development of long, narrow, branching filaments in the early stages of growth. In the accepted sense of Actinomyces at the time, this view was very plausible, especially as the colonies on solid media greatly resemble those of many aerobic actinomycetes. In suggesting this relationship, however, no account was taken of either the longitudinal septation or the extraordinarily close spacing of the first few transverse septa to give segments with their long axes across the filament. The transfer of A. dermatonomus to Nocardia has already been discussed and the arguments outlined are equally applicable to Dermatophilus congolensis and Polysepta pedis.

The one character however which sets Dermatophilus apart from most of the actinomycetes is the possession of motile spores. These have been described by Thompson (1954) in Polysepta pedis as oval, less than 1.0μ in diameter, and apically flagellate with a variable number of flagella. Simmons (1955) pointed out the existence of such spores in A. dermatonomus and stressed their importance in the life history of this species. In D. congolensis there has never been an adequate description of the occurrence of motile spores even though they are easily seen in

cultures. Van Saceghem (1934), however, may well have seen them when he stated that: "Examiné à frais le tétragène est immobile, c'est-à-dire qu'il ne présente pas de mouvements de translation; par contre, il est animé d'un mouvement de va et vient très accentué qui n'a rien de commun avec le mouvement brownien".

Although the occurrence of motile spores is of great importance in the classification of these organisms, it is their mode of formation and release which may clinch their relationships in the end. It is clear that the transverse and longitudinal septation is the first stage in the formation of spores. There follows a stage in which the contents of each segment become more refractive and within a short time the spore is ready for release. Thompson (1954) and Thompson & Bisset (1957), to whom knowledge of the motile spore is mostly due, seem to indicate that they believe the filaments simply break up and each segment becomes a motile coccus, forming its flagella on its outer wall. An alternative to this method would be for the divided filaments to act as multilocular sporangia, each segment releasing a single spore through a pore or by the rupture of the outer wall. Van Saceghem (1934, p. 592) again has some observations which may have some bearing on this for he says that: "les granulations inclues dans les filaments quittent ceux-ci dont on ne retrouve plus que des lambeaux dans lesquels l'on peut observer encore un semblant d'organisation qui correspond à la place précédemment occupée par les granulations". Thus it would seem that the filament is acting as a sporangium in this case. The situation probably requires electron microscopy of carefully prepared material to decide this point, which is of vital importance. The exact nature of the motile cells is therefore not clear at the present time. They may correspond to the motile swarmers of certain bacteria but it is also possible that they are isogametes, although the evidence for this is uncertain. They are referred to here as "spores" by analogy to the motile haploid and diploid zoospores of chytridiaceous fungi, and are not in any way comparable to the resistant bacterial spore.

Jensen (1953) discussed the evidence for motility in Nocardia and concluded that certain species produce motile rods or cocci, whilst recent studies by Couch (1949, 1954) have revealed the existence of actinomycetes placed in the genus Actinoplanes and closely related to Streptomyces, which form motile spores within minute terminal sporangia. It is thus possible to include organisms with motile spores within the Actinomycetales without creating a precedent and Jensen has already suggested that the definition of the order should be altered to include motility as an occasional character.

Because the characters of Dermatophilus are so distinct it is proposed that the genus should be placed in a new family of the Actinomycetales under the Group B I of Waksman & Henrici (1943) next to the Actinomycetaceae. In this way it would be analogous to the Actinoplanaceae (Couch, 1955) tentatively placed here in Group B II.

NOMENCLATURAL PROPOSALS

As the main purpose of this paper is to attempt to provide a sound

nomenclatural basis for current usage, it is necessary to put forward certain proposals based on both published work and to a small extent on unpublished personal observations on clinical material and isolates*. Such proposals must be regarded as tentative until all the species concerned have been thoroughly studied:

The formal diagnoses proposed are:-

Order ACTINOMYCETALES Buchanan 1917-1918.

Family DERMATOPHILACEAE fam. nov.

Mycelial filaments dividing transversely and longitudinally to form motile cocci. Pathogenic organisms causing skin lesions in mammals.

Genus Dermatophilus Van Saceghem 1915 emend. 1916, 1934.

Mycelium of narrow, tapering filaments with lateral branching at right angles; septa formed in transverse and in horizontal and vertical longitudinal planes, giving rise to up to eight parallel rows of coccoid cells which form motile flagellate spores. Species pathogenic for mammals including cattle, sheep, horses, goats and experimentally for rabbits, guinea-pigs and mice; causing exudative or pustular dermatitis. Aerobic and weakly fermentative.

Syn. Dermatophylus Van Saceghem 1914; Polysepta Thompson & Bisset 1957.

Type species — D. congolensis Van Saceghem 1915.

Dermatophilus congolensis Van Saceghem 1915.

Syn. Actinomyces congolensis (Van Saceghem) Hudson 1937; (nec (Baerts) Brumpt 1927): Streptothrix bovis Snijders & Jansen 1955; (nec (Harz) Chester 1901; Foulerton 1901): Tetragenus congolensis Van Saceghem 1934.

Morphological characters as genus —

Mycelial filaments non-septate at apices, 0.5μ–1.5μ diameter, up to 5.0μ wide after several transverse and longitudinal divisions. Colonies on solid media rough or smooth, greyish white becoming yellowish with age and sometimes viscous. Coagulates litmus milk;

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* See appendix. (p. 48).

liquefaction of gelatin begins on sixth day. Grows well at 37°C. Mycelium and spores Gram positive. Pellicle sometimes formed on liquid media. Fermentation with acid after 48 hours in glucose, sucrose, maltose, and dextrin. No fermentation of lactose, mannite, sorbite, laevulose, galactose, dulcite or arabinose. Causes streptothricosis in cattle, horse, sheep, goat and eland.

Dermatophilus dermatonomus (Bull 1929) Austwick 1958.
Syn. Nocardia dermatonomus (Bull) Henry 1952; Polysepta dermatonomus (Bull) Thompson & Bisset 1957.
Morphological characters as genus —
Mycelial filaments 0.5μ–1.5μ diameter, up to 5.0μ wide after several transverse and longitudinal divisions.
Colonies on peptone agar at 37°C. raised, convex, smooth, Antimony yellow (Ridgeway), becoming mucoid when moist. At 22°C. colony rough. Liquefies gelatin at pH 7.6 in six days. Produces pellicle on peptone broth. Litmus milk decolorized in four days, digested in six. Mycelium and spores Gram positive.
Fermentation with acid in glucose, laevulose and galactose.
Causes mycotic dermatitis in sheep.

Dermatophilus pedis (Thompson & Bisset 1957) comb. nov.
Syn. Polysepta pedis Thompson & Bisset 1957; Rhizobium sp. Thompson 1954.
Morphological characters as genus —
Colony on solid media at first grey, rough, adherent to medium, later yellowish, smooth and moist and no longer adherent.
Does not liquefy gelatin or coagulate serum. Gram positive.
Fermentation with acid only in glucose and mannitol. No fermentation in galactose.
Causes strawberry foot rot in sheep.

Disease names

If the nomenclature outlined above should prove acceptable it will be necessary to safeguard the well-known clinical names of these diseases against the use of new terms based on the valid names of the causal organisms. Sooner or later for instance "dermatophilosis" will be suggested and although an admirable "generic" name to cover these diseases, it will become yet another confusing term if applied indiscriminately to different hosts.

"Cutaneous streptothricosis" remains the most useful name for the disease in cattle, providing "nocardiosis" and not "streptothricosis" becomes generally adopted for the respiratory and systemic diseases caused by aerobic actinomycetes belonging to Nocardia. "Mycotic dermatitis", despite the possibility of its wide interpretation, has become conveniently restricted to the disease of sheep, whilst "strawberry foot rot" is so aptly descriptive that it warrants continued usage. The dermatitis described by Nisbet & Bannatyne (1955), although a clear cut entity, has not yet received a specific clinical name.

DISCUSSION

It remains to be seen whether these three species are sufficiently different from one another to be taxa of this rank or whether two of them are really of a lower category. A distinct form of D. congolensis has for instance been reported by Stableforth (1937) from a horse which, in experimental inoculation in rabbits produced a pustular type of reaction instead of the more common generalized erythema and exudation. The chief need at present is for a close examination of the characteristics and stability of the known strains by means of single spore isolates and the isolation of a large number of new strains from affected animals to determine the natural range of variation.

SUMMARY

The histories of bovine cutaneous streptothricosis and of mycotic dermatitis and strawberry foot rot in sheep are reviewed, and the relationships of the causal organisms discussed. The organisms are considered to be congeneric and Dermatophilus the earliest generic name for them. Three species are recognized – D. congolensis from streptothricosis in cattle, D. dermatonomus from mycotic dermatitis in sheep and D. pedis comb. nov. from strawberry foot rot of sheep. The genus is placed in a new family -- the Dermatophilaceae of the Actinomycetales.

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APPENDIX

Isolates of Dermatophilus studied

No.	Nature	Source	Date of Isolation	Received
	D. congolensis group.			
V. 1103	Primary isolate	From cattle, N. Rhodesia, isolated by J. R. Hudson.	1955	25. 1.56.
*V. 1239	Culture N.C.T.C. 5170	From cattle, Kenya, isolated by J. R. Hudson. (contaminated)	1937	29. 8.56.
V. 1240	Culture N.C.T.C. 5175	From horse, Great Britain, isolated by A. W. Stableforth.	1937	29. 8.56.
V. 1328	Primary isolate	From cattle, N. Rhodesia comm. by S. A. Hutchings, isolated by P. K. C. Austwick.	1956	29.11.56.
V. 1375	Culture	From cow, Khartoum, Republic of the Sudan, isolated by K. N. Soliman.	1957	21. 1.57.
V. 1402	Culture S. 13/1	From cattle, Northern Nigeria isolated by I. MacAdam.	1957.	13. 2.57.
	D. dermatonomus group.			
*V. 248	Culture	From sheep, Victoria, Australia, comm. by L. B. Bull.	–	15.10.52.

*not retained in culture (11. 6. 57).

No.	Nature		Date of Isolation	Received
*V. 292	Culture	From sheep, Union of South Africa, comm. by R. A. Alexander	–	1.12.52.
*V. 688	Culture	From sheep, Union of South Africa, comm. by C. B. Hart.	–	18. 2. 54.
* –	Culture	From sheep, Argentine, comm. by C. N. Ault, Buenos Aires.	–	5. 2.54.
V. 973	Culture	From sheep (face lesions) Scotland, comm. by D. I. Nisbet.	1954	13.10.55.
V. 1104	Culture	From sheep, Herefordshire, England, comm. by G. J. Kane.	1955	26. 1.56.
*V.1118	Culture G2778	From sheep, Queensland, Australia, comm. by G. Simmons.	–	17. 2.56.
*V. 1119	Culture H 138	From sheep, Queensland, Australia, comm. by G. Simmons.	–	17.2.56.
V. 1264	Culture	From sheep, England, comm. by G. J. Kane.	1956	10. 9.56.

* not retained in culture (11. 6. 57).

Rinderpest: Some Notes on Control by Modified Virus Vaccines. III

BY

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THE MODIFIED VIRUS VARIANTS OF RINDERPEST

III. Avianized Rinderpest Virus (Virus adapted to the chick embryo)

While considerable information derived from laboratory studies has been available since 1946 from the Grosse Isle team of American-Canadian workers and from Nakamura and his colleagues in Japan, there is still very little known about the capabilities of the avianized virus vaccine in the field.

History

An attempt to cultivate the virus of rinderpest on the chorio-allantoic membrane of the chick embryo was made in Tanganyika by Kunnert (1938), using eight-day embryos and harvesting the membranes five to seven days later. Virus remained infective in the egg for five days when tested in calves, but transmission in series was never accomplished.

Successful cultivation was first reported in 1946 by Shope, Griffiths & Jenkins, together with other investigations made during the second world war by the American-Canadian Rinderpest Commission at Grosse Isle on the St. Lawrence river. Walker (1947) made 36 serial passages in the chick embryo of a virus which had been alternated five times between rabbits and calves but was unable to grow, on the chick embryo, a virus which had had 65 rabbit passages. Nakamura, Sato & Miyamoto (1947) obtained multiplication of Nakamura III lapinized virus in the chick-embryo spleen after intravenous injection, but were able to maintain it in the embryo, only after eleven alternate chorio-allantoic and rabbit passages (Nakamura & Miyamoto, 1953). A bovine strain of virus (Kabete "O") was adapted to the chick embryo by Cheng, Chow & Fischman (1949) and this confirmed the work at Grosse Isle, while Ishii & Tsukuda (1952) passaged in eggs the strain of bovine virus from which originated the Nakamura III lapinized variant.

Strains of virus from two distinct sources, namely from the ox and an attenuated virus adapted to the rabbit, have been induced to multiply in the tissues of the chick embryo. Most of the information about avianized virus is limited to the publications quoted; the most complete records at this time are those of the American-Canadian Rinderpest Commission.

Origin of avianized virus

It appears that rinderpest virus does not behave uniformly since some strains are able to grow in chick-embryo tissues while others grow on the membranes but do not invade the embryo. The Grosse Isle workers tried a number of strains but were successful only with the East African virus, while Cheng et al. (1949) reported that two Chinese viruses and one from North Africa failed to grow. Success appears to have followed the use of virus which had been maintained experimentally for long periods in cattle or after some stress likely to affect stability, such as passage in the rabbit. Furthermore, preliminary growth on the chorio-allantoic (C.A.) membrane was required before the virus could be induced to invade the tissues of the embryo proper; this was achieved by changing the route of inoculation to the yolk sac. The Kabete "O" virus required seven to ten such passages, an Indian virus grown by Cheng et al. would not transfer after 30 serial passages on the C.A. membrane, while the Japanese workers experienced difficulty in infecting embryos via the yolk sac before the 70th passage on the C.A. membrane.

According to Shope et al., a second adaptation occurred after transfer to the yolk sac, for in early passages, the virus required 48 to 72 hours in which to invade the embryo, but later this was reduced to 24 hours. For C.A. passage, eight to ten-day embryonated eggs were used, harvested three to five days later, while for yolk sac passage, six to seven-day eggs were most suitable, harvested at 48 to 96 hours. The most favourable incubation temperature was 37° to 39° C. It has been suggested that incubation at 35° C. or the use of eight-day eggs harvested five days later, resulted in a more rapid attenuation of the virus for cattle. Nakamura, Kishi & Miyamoto (1954), in another description of the cultivation of lapinized virus in the chick embryo, compared the effects of various routes of inoculation. They found the best yield in 12-day embryos inoculated intravenously, harvested 5 to 6 days later and by yolk sac inoculation in 5-day embryos harvested at 7–9 days.

Virulence of the virus

Passage of the bovine virus in embryonated eggs did not result in the appearance of macroscopic lesions but some embryos died between the second and fourth day after inoculation. Work in progress at E.A.V.R.O., Kenya (1957) has suggested that such mortality may be reduced by neutralizing the virus with immune serum but the precise role of the virus requires to be investigated further. In embryos inoculated via the yolk sac, virus has been demonstrated up to and after hatching and surviving embryos, although heavily infected, appeared normal. Shope et al. have provided some evidence for increasing pathogenicity for the embryo after 33 passages in the yolk sac but the change was not accompanied by any increase in titre of virus.

The Japanese workers have reported that lapinized virus adapted to the egg has resulted in an increase in the spleen/embryo weight ratio and claimed that infectivity for the embryo increased; Nakamura & Kishi (1954) reported that lapinized-avianized virus lost all infectivity for the

chick embryo after return to the rabbit for 15 passages.

Bovine rinderpest virus maintained on the C.A. membrane, retains its pathogenicity for cattle for considerable periods varying from 69 to over 313 serial passages at which stage it has been reported to cause severe reactions in Japanese cattle. After yolk sac passage, the virus becomes attenuated rapidly to the stage when it becomes safe as a vaccine for cattle; according to Shope et al., this became evident at the 43rd yolk sac passage, the number of transfers was important for if transferred at three to four-day intervals attenuation was slow but at 48-hour intervals the rate was increased. In Japan, calves tested with 51 to 179 yolk sac passages of bovine virus survived and were immune.

It is difficult to compare results of the Western and Eastern workers at this stage of research because of the recognized variation in resistance and susceptibility of the test cattle; a virus might be of low virulence for cattle of European breeds and still highly pathogenic for Japanese cattle, while in reverse, an Eastern virus of low virulence might be unable to multiply in more resistant cattle.

Hale & Walker (1946) were able to increase the virulence of avianized virus for their test cattle after six direct transfers in calves and at this stage the virus was contagious. The haematology of cattle infected with avianized virus in the early stages of embryo passage, has been studied by Takematsu & Morimoto (1955). They reported a leucopenia which gradually returned to normal, a neutrophilic shift to the left and a striking increase in monocytes. These changes became less apparent after the 21st embryo passage of the virus.

Properties of the virus

After a variable number of passages in the embryo, bovine virus may be sufficiently attenuated to be used as a live avirulent vaccine. Cattle may react to a mild degree and are unable to transmit infection to susceptible calves by contact. A viraemia is established after vaccination and early protection by means of the interference phenomenon has been demonstrated. In the fresh state, the virus is fragile, but it can be freeze-dried and in this state or when frozen it remains viable for long periods at low temperature (Daubney, 1957). Avianized rinderpest virus appears to conform to the pattern of the other attenuated viruses but more information is required before its usefulness can be compared with theirs.

For example, it has been suggested that there is some danger in over-attenuation of the virus by passage in the yolk sac of the embryo and there has been little practical experience of the properties of the virus in cattle of varying susceptibility and resistance to rinderpest. Recently, Piercy & Witcomb (1957), working at Muguga, Kenya, have described experiments with a Japanese avianized virus. They report that 1 g. of freeze-dried whole egg will immunize 50% of cattle at a dilution of 10^{-6}. When reconstituted from the dried state, virus suffered no loss in titre after six hours at 20° C. but was reduced a hundredfold after 24 hours. When kept at 30° C. for two and six hours the loss in titre was tenfold; at 40° C. it was tenfold after one hour and after three hours it was one hundredfold. Dried whole egg vaccine in ampoules after storage for

seven days at 30° C. dropped in titre by tenfold and by fivefold after storage for ten days at 20° C. and nine months at minus 25° C. These results compared very favourably with those described for other attenuated rinderpest vaccines and showed that there would be a workable safety margin when using an avianized vaccine under field conditions. There are few reports of its use as a vaccine in the field apart from those of Cheng et al. (1949) and Daubney (1953) and while Reisinger, Mun & Lee (1954) described the vaccination of Korean cattle with lapinized-avianized virus, the duration of immunity has not been investigated experimentally or under field conditions. According to Ishii & Kurata (1954), complement-fixing antibodies can be detected in the sera of hyperimmune cattle, using an antigen from the yolk sac of embryos infected with avianized virus, while Furutani, Nakamura, Ishii & Kurata (1954) have described a virus-neutralizing test in embryonated eggs. Working in Korea, with cattle vaccinated with lapinized-avianized virus, Nakamura, Kishi, Kiuchi & Reisinger (1955) demonstrated the presence of complement-fixing antibodies in over 60% of sera, the majority of which also gave evidence of neutralizing antibodies.

Avianized virus as vaccine

The need for an efficient vaccine of low pathogenicity for use in highly susceptible cattle stimulated research in the Far East, particularly in Japan, where the majority of the cattle were very susceptible to rinderpest. The lapinized-avianized variant developed by Nakamura et al. was dictated by necessity, for the lapinized virus was fixed in virulence for cattle at a level unsuitable for use in Japanese cattle without an immune serum to control the reaction. In the West, where lapinized virus has been introduced to immunize cattle in which the more active goat-virus was unsuitable, the attraction of the avianized virus lies in the possibility it offers of a cheap vaccine produced with standardized techniques so that the pathogenicity may be controlled at levels to suit the varying resistance of different types of cattle.

Daubney (1947) remarked that the flexibility of avianized virus was one of its major attributes and Danks (1950) reported a good immunity in cattle challenged 17 months after inoculation in Kenya. Preliminary experiments by Piercy & Witcomb (1957) have shown that a cheap and effective avianized vaccine can be produced with good keeping qualities and the advantage of inducing thermal reactions in 80% of medium grade crossbred European zebu cattle in Kenya. However, research on the virus has been neglected since the first reports while the caprinized and lapinized vaccines have been proved in the field during the interim. When one recalls the volume of research, labour and field experience expended and the lapse of time between the first experiences in India and the present world-wide application of goat-adapted virus, it becomes clear that experiments with avianized virus must be planned and assessed carefully before a third type of vaccine is introduced.

It is doubtful if the original antigenic strain of egg-adapted virus developed by the American/Canadian workers is still in existence, but the Japanese avianized virus is under investigation in Japan and at

E.A.V.R.O., Kenya (1956, 1957) and progress will be anticipated by all concerned with control of rinderpest. Clearly independent research is essential in the development of a vaccine with the potentiality which has been attributed to avianized virus. Should it ever prove practicable to use avianized viruses of graduated potencies instead of other live attenuated vaccines, e.g. goat and rabbit adapted, then the time would be opportune for production to agreed International standards, combined with co-operation in an attempt to eradicate rinderpest.

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